Dossier zur Nutzenbewertung gemäß § 35a SGB V

Selumetinib (Koselugo®)

Alexion Pharma Germany GmbH

Anhang 4-G3

Studie KOMET
2. Datenschnitt vom 05. August 2024 –
weitere Auswertungen

Stand: 04.02.2026

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Anhang 4-G3 Studie KOMET 2. Datenschnitt vom 05. August 2024 – weitere Auswertungen

1 Subgruppenanalysen

1.1 Endpunktkategorie Morbidität

1.1.1 Endpunkt Volumenänderung der Zielläsion

1.1.1.1 Volumenänderung der Zielläsion – Absolute Volumenänderung der Zielläsion im Vergleich zu Baseline – Zyklus 12, Tag 28 und über die randomisierte Phase

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 7.8.1.4 Change from Baseline in Target PN Volume (mL) by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	532.88 (778.20)						
	Placebo (N=74)	9 (12.16%)	836.02 (1825.10)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	2 (2.82%)	-80.07 (112.49)	-86.61 (6.76)	(-108.14, -65.09)	-8.55 (-35.18, 18.07)	0.382		0.745
	Placebo (N=74)	6 (8.11%)	-1.77 (13.48)	-78.06 (6.52)	(-98.80, -57.33)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	-65.32 (76.24)	-106.96 (23.65)	(-155.77, -58.16)	-55.27 (-109.16, -1.38)	0.045	-0.68 (-1.93 ,0.57)	0.239
	Placebo (N=74)	9 (12.16%)	10.52 (49.99)	-51.69 (28.47)	(-110.46, 7.07)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subjects with missing ethnicity are excluded.
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Table 7.8.1.4 Change from Baseline in Target PN Volume (mL) by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	63 (88.73%)	498.72 (1288.77)					
	Placebo (N=74)	63 (85.14%)	507.39 (751.40)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	46 (64.79%)	-56.03 (202.42)	-69.75 (16.17)	(-101.92, -37.59)	-77.79 (-120.05, -35.53)	<0.001	-0.71 (-1.14 ,-0.28)
	Placebo (N=74)	45 (60.81%)	5.59 (76.37)	8.04 (15.82)	(-23.42, 39.49)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	57 (80.28%)	-44.96 (185.67)	-46.62 (10.45)	(-67.19, -26.06)	-54.21 (-80.41, -28.01)	<0.001	-0.69 (-1.07 ,-0.32)
	Placebo (N=74)	60 (81.08%)	8.35 (90.84)	7.59 (9.88)	(-11.86, 27.04)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subjects with missing ethnicity are excluded.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 7.8.1.5 Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: North America

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	761.61 (2053.25)						
	Placebo (N=74)	6 (8.11%)	307.86 (660.80)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	-21.68 (50.65)	-26.30 (16.51)	(-66.71, 14.11)	-21.89 (-80.56, 36.77)	0.396		0.455
	Placebo (N=74)	5 (6.76%)	-3.36 (14.82)	-4.41 (17.07)	(-46.18, 37.36)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	-94.69 (278.66)	-59.92 (7.85)	(-75.97, -43.86)	-24.07 (-46.57, -1.57)	0.037	-1.02 (-2.23 ,0.20)	0.606
	Placebo (N=74)	6 (8.11%)	-17.01 (48.57)	-35.84 (8.18)	(-52.56, -19.12)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.5 Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Europe

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	456.99 (1094.74)					
	Placebo (N=74)	27 (36.49%)	534.21 (861.21)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	19 (26.76%)	-38.86 (161.00)	-51.76 (30.87)	(-114.65, 11.13)	-81.86 (-166.26, 2.54)	0.057	
	Placebo (N=74)	17 (22.97%)	15.73 (118.45)	30.10 (30.26)	(-31.53, 91.73)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	25 (35.21%)	-19.93 (139.15)	-19.01 (16.44)	(-51.55, 13.53)	-40.34 (-82.20, 1.51)	0.059	
	Placebo (N=74)	26 (35.14%)	11.91 (106.63)	21.33 (15.87)	(-10.08, 52.74)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.5 Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Asia

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	18 (25.35%)	525.83 (1451.26)					
	Placebo (N=74)	21 (28.38%)	549.80 (722.09)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	-114.16 (293.77)	-104.23 (25.32)	(-155.95, -52.52)	-94.58 (-159.39, -29.76)	0.006	-0.92 (-1.64 ,-0.19)
	Placebo (N=74)	19 (25.68%)	0.94 (42.19)	-9.65 (23.11)	(-56.86, 37.55)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	-74.34 (215.43)	-69.95 (16.49)	(-102.68, -37.22)	-77.95 (-118.83, -37.07)	<0.001	-1.13 (-1.86 ,-0.41)
	Placebo (N=74)	20 (27.03%)	9.33 (82.78)	8.00 (14.94)	(-21.66, 37.67)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.5 Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	322.73 (511.92)					
	Placebo (N=74)	20 (27.03%)	605.42 (1266.07)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-5.52 (15.84)	-2.45 (5.29)	(-13.55, 8.66)	-9.80 (-22.82, 3.22)	0.131	
	Placebo (N=74)	12 (16.22%)	2.13 (13.92)	7.35 (5.11)	(-3.39, 18.09)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	14 (19.72%)	-17.60 (45.91)	-19.89 (12.75)	(-45.28, 5.50)	-32.31 (-58.72, -5.90)	0.017	-0.65 (-1.38 ,0.09)
	Placebo (N=74)	19 (25.68%)	12.99 (64.88)	12.42 (11.33)	(-10.14, 34.98)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.6 Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	13 (18.31%)	393.80 (830.95)						
	Placebo (N=74)	18 (24.32%)	890.51 (1355.95)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	10 (14.08%)	-48.99 (201.43)	83.29 (94.05)	(-121.62, 288.21)	-44.92 (-202.22, 112.39)	0.545		0.132
	Placebo (N=74)	9 (12.16%)	55.67 (109.98)	128.21 (69.55)	(-23.33, 279.75)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-40.92 (150.17)	-24.87 (40.92)	(-106.72, 56.98)	-71.94 (-141.38, -2.49)	0.043	-0.53 (-1.34 ,0.28)	0.050
	Placebo (N=74)	17 (22.97%)	29.78 (130.15)	47.07 (31.76)	(-16.47, 110.61)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.8.1.6 Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	255.95 (526.11)					
	Placebo (N=74)	12 (16.22%)	325.80 (362.53)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	-7.04 (14.04)	-18.47 (11.98)	(-44.36, 7.41)	-12.64 (-44.79, 19.50)	0.411	
	Placebo (N=74)	11 (14.86%)	-5.36 (37.08)	-5.83 (9.98)	(-27.39, 15.73)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	-22.35 (47.58)	-40.58 (10.85)	(-62.34, -18.82)	-48.37 (-74.40, -22.35)	<0.001	-1.36 (-2.31 ,-0.41)
	Placebo (N=74)	12 (16.22%)	13.76 (57.14)	7.79 (8.89)	(-10.03, 25.62)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.8.1.6 Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	1311.29 (2283.34)					
	Placebo (N=74)	11 (14.86%)	781.94 (902.99)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	-136.20 (339.55)	-141.87 (40.69)	(-229.15, -54.59)	-155.26 (-269.45, -41.06)	0.011	-1.02 (-2.01 ,-0.04)
	Placebo (N=74)	9 (12.16%)	21.42 (46.93)	13.39 (50.61)	(-95.15, 121.93)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	15 (21.13%)	-107.75 (320.27)	-86.19 (35.30)	(-156.88, -15.50)	-88.82 (-186.47, 8.83)	0.074	
	Placebo (N=74)	11 (14.86%)	30.25 (111.21)	2.63 (45.82)	(-89.12, 94.37)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.8.1.6 Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	30 (42.25%)	165.77 (250.37)					
	Placebo (N=74)	32 (43.24%)	304.04 (706.53)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-27.32 (78.41)	-41.08 (11.51)	(-64.43, -17.73)	-27.28 (-56.65, 2.10)	0.068	
	Placebo (N=74)	23 (31.08%)	-13.64 (66.88)	-13.80 (10.88)	(-35.87, 8.27)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	-18.17 (61.24)	-26.32 (5.03)	(-36.27, -16.36)	-17.30 (-29.54, -5.06)	0.006	-0.65 (-1.19 ,-0.10)
	Placebo (N=74)	30 (40.54%)	-7.29 (42.45)	-9.02 (4.84)	(-18.58, 0.54)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.8.1.7 Change from Baseline in Target PN Volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	29 (40.85%)	22.55 (16.26)						
	Placebo (N=74)	19 (25.68%)	28.32 (12.71)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	21 (29.58%)	-2.04 (4.65)	-2.87 (1.45)	(-5.85, 0.10)	-1.84 (-5.65, 1.97)	0.331		0.000
	Placebo (N=74)	13 (17.57%)	0.23 (5.64)	-1.03 (1.73)	(-4.58, 2.51)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	-1.85 (3.60)	-2.49 (0.60)	(-3.67, -1.31)	-2.32 (-3.80, -0.83)	0.003	-0.74 (-1.39 ,-0.10)	0.000
	Placebo (N=74)	17 (22.97%)	0.80 (4.11)	-0.17 (0.73)	(-1.61, 1.27)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.7 Change from Baseline in Target PN Volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	24 (33.80%)	145.73 (74.28)					
	Placebo (N=74)	25 (33.78%)	165.03 (89.91)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-17.04 (55.36)	-20.97 (12.57)	(-46.55, 4.60)	-20.10 (-46.72, 6.52)	0.134	
	Placebo (N=74)	20 (27.03%)	-0.81 (19.92)	-0.88 (11.10)	(-23.45, 21.70)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	-14.76 (39.64)	-16.53 (6.17)	(-28.75, -4.31)	-20.14 (-32.49, -7.80)	0.002	-0.72 (-1.32 ,-0.11)
	Placebo (N=74)	25 (33.78%)	3.77 (29.21)	3.62 (5.30)	(-6.88, 14.11)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.7 Change from Baseline in Target PN Volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	18 (25.35%)	1666.29 (2055.91)					
	Placebo (N=74)	30 (40.54%)	1175.38 (1202.95)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	10 (14.08%)	-235.02 (393.97)	-198.98 (54.45)	(-311.61, -86.34)	-189.52 (-312.67, -66.36)	0.004	-1.09 (-1.94 ,-0.24)
	Placebo (N=74)	20 (27.03%)	15.37 (114.99)	-9.46 (37.48)	(-87.00, 68.08)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	-159.26 (332.35)	-175.29 (30.48)	(-235.73, -114.85)	-168.43 (-242.38, -94.48)	<0.001	-1.37 (-2.06 ,-0.67)
	Placebo (N=74)	29 (39.19%)	18.18 (132.31)	-6.86 (22.42)	(-51.31, 37.59)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.8 Change from Baseline in Target PN Volume (mL) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	21 (29.58%)	642.17 (1114.51)						
	Placebo (N=74)	21 (28.38%)	667.47 (744.42)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	13 (18.31%)	-65.41 (114.79)	-76.09 (30.42)	(-139.02, -13.15)	-70.84 (-153.52, 11.84)	0.090		0.586
	Placebo (N=74)	16 (21.62%)	6.40 (88.25)	-5.25 (27.95)	(-63.06, 52.57)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	-43.60 (128.11)	-54.28 (18.83)	(-91.69, -16.87)	-65.36 (-112.27, -18.45)	0.007	-0.83 (-1.52 ,-0.14)	0.653
	Placebo (N=74)	21 (28.38%)	19.27 (121.41)	11.08 (16.83)	(-22.35, 44.51)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.8 Change from Baseline in Target PN Volume (mL) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	50 (70.42%)	413.18 (1281.36)					
	Placebo (N=74)	53 (71.62%)	488.84 (992.28)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	38 (53.52%)	-49.57 (214.77)	-59.41 (14.70)	(-88.73, -30.10)	-69.34 (-108.55, -30.13)	<0.001	-0.77 (-1.25 ,-0.30)
	Placebo (N=74)	37 (50.00%)	5.18 (63.56)	9.93 (14.28)	(-18.56, 38.42)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	48 (67.61%)	-44.22 (190.04)	-50.61 (8.76)	(-67.86, -33.37)	-55.48 (-77.97, -32.99)	<0.001	-0.92 (-1.34 ,-0.49)
	Placebo (N=74)	50 (67.57%)	4.34 (64.42)	4.87 (8.41)	(-11.70, 21.44)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.9 Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	194.72 (271.17)						
	Placebo (N=74)	13 (17.57%)	452.40 (689.71)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	10 (14.08%)	-35.01 (65.19)	-36.69 (15.12)	(-68.60, -4.78)	-39.19 (-78.59, 0.22)	0.051		0.059
	Placebo (N=74)	11 (14.86%)	-6.83 (37.12)	2.49 (14.77)	(-28.67, 33.66)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-25.60 (52.13)	-30.77 (12.03)	(-54.87, -6.67)	-28.48 (-58.81, 1.85)	0.065		0.167
	Placebo (N=74)	12 (16.22%)	14.89 (104.01)	-2.29 (11.62)	(-25.58, 21.00)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.9 Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	7 (9.86%)	1046.15 (2308.25)					
	Placebo (N=74)	8 (10.81%)	708.08 (792.49)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	6 (8.45%)	-246.07 (466.74)	-207.62 (57.29)	(-335.26, -79.98)	-169.83 (-336.68, -2.99)	0.047	-1.09 (-2.36 ,0.18)
	Placebo (N=74)	8 (10.81%)	11.63 (48.82)	-37.79 (52.85)	(-155.55, 79.98)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	6 (8.45%)	-158.28 (338.30)	-136.52 (23.67)	(-184.73, -88.30)	-106.79 (-169.82, -43.76)	0.002	-1.66 (-3.04 ,-0.28)
	Placebo (N=74)	8 (10.81%)	1.47 (36.72)	-29.73 (21.84)	(-74.21, 14.76)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.9 Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	31 (43.66%)	448.70 (1039.33)					
	Placebo (N=74)	30 (40.54%)	505.37 (824.75)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	-33.17 (149.88)	-43.87 (27.31)	(-99.17, 11.42)	-72.41 (-144.08, -0.74)	0.048	-0.57 (-1.21 ,0.06)
	Placebo (N=74)	20 (27.03%)	14.94 (108.83)	28.54 (26.54)	(-25.19, 82.27)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-16.92 (130.79)	-14.96 (14.82)	(-44.26, 14.34)	-36.34 (-72.97, 0.28)	0.052	
	Placebo (N=74)	29 (39.19%)	11.73 (100.02)	21.38 (14.30)	(-6.89, 49.66)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.9 Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	489.54 (1341.46)					
	Placebo (N=74)	23 (31.08%)	574.71 (1216.23)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	13 (18.31%)	-13.67 (32.08)	-16.66 (6.41)	(-29.92, -3.39)	-16.19 (-34.70, 2.33)	0.084	
	Placebo (N=74)	14 (18.92%)	-1.61 (13.29)	-0.47 (6.29)	(-13.48, 12.54)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-54.86 (187.71)	-51.28 (16.20)	(-83.42, -19.13)	-60.04 (-100.36, -19.72)	0.004	-0.84 (-1.49 ,-0.19)
	Placebo (N=74)	22 (29.73%)	4.46 (66.76)	8.76 (14.49)	(-20.00, 37.52)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.1 Change from Baseline in Target PN Volume (mL) by Age Group (Full Analysis Set)
Age Group: 18 - <30

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	32 (45.07%)	140.28 (146.87)						
	Placebo (N=74)	42 (56.76%)	499.71 (746.03)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	23 (32.39%)	-2.21 (31.27)	-9.83 (17.08)	(-44.16, 24.50)	-21.62 (-63.25, 20.02)	0.302		0.933
	Placebo (N=74)	33 (44.59%)	5.26 (88.51)	11.79 (13.36)	(-15.05, 38.63)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-3.77 (26.98)	-5.95 (8.43)	(-22.58, 10.67)	-20.26 (-40.09, -0.43)	0.045	-0.46 (-0.96 ,0.03)	0.626
	Placebo (N=74)	41 (55.41%)	13.45 (78.44)	14.31 (6.59)	(1.30, 27.32)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.1 Change from Baseline in Target PN Volume (mL) by Age Group (Full Analysis Set)
Age Group: 30 - <65

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	39 (54.93%)	760.40 (1611.16)					
	Placebo (N=74)	32 (43.24%)	591.79 (1132.94)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-95.83 (253.50)	-81.80 (18.85)	(-119.88, -43.73)	-66.23 (-118.59, -13.86)	0.014	-0.65 (-1.26 ,-0.05)
	Placebo (N=74)	20 (27.03%)	6.03 (24.65)	-15.58 (22.43)	(-60.88, 29.72)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	37 (52.11%)	-75.71 (228.91)	-69.72 (16.55)	(-102.41, -37.02)	-55.62 (-99.07, -12.17)	0.012	-0.53 (-1.03 ,-0.03)
	Placebo (N=74)	30 (40.54%)	1.86 (95.28)	-14.10 (19.29)	(-52.20, 24.00)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.2 Change from Baseline in Target PN Volume (mL) by Sex (Full Analysis Set)
Sex: Male

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	33 (46.48%)	601.79 (1509.24)						
	Placebo (N=74)	42 (56.76%)	625.19 (879.40)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	26 (36.62%)	-66.34 (241.09)	-74.28 (25.77)	(-126.09, -22.48)	-89.32 (-152.58, -26.05)	0.007	-0.66 (-1.22 ,-0.10)	0.342
	Placebo (N=74)	29 (39.19%)	6.18 (89.87)	15.03 (25.02)	(-35.28, 65.34)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	31 (43.66%)	-64.54 (218.29)	-53.92 (15.35)	(-84.21, -23.64)	-73.50 (-109.71, -37.28)	<0.001	-0.81 (-1.31 ,-0.32)	0.214
	Placebo (N=74)	40 (54.05%)	6.89 (107.78)	19.58 (14.56)	(-9.16, 48.31)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.2 Change from Baseline in Target PN Volume (mL) by Sex (Full Analysis Set)
Sex: Female

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	38 (53.52%)	375.93 (934.03)					
	Placebo (N=74)	32 (43.24%)	427.09 (989.35)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	25 (35.21%)	-40.37 (129.99)	-48.00 (15.50)	(-79.29, -16.71)	-50.67 (-91.77, -9.57)	0.017	-0.67 (-1.26 ,-0.08)
	Placebo (N=74)	24 (32.43%)	4.79 (39.61)	2.67 (14.37)	(-26.34, 31.67)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	34 (47.89%)	-23.34 (115.21)	-35.41 (10.00)	(-55.16, -15.66)	-39.60 (-64.70, -14.51)	0.002	-0.71 (-1.22 ,-0.20)
	Placebo (N=74)	31 (41.89%)	11.14 (46.64)	4.19 (9.16)	(-13.89, 22.28)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.8.1.3 Change from Baseline in Target PN Volume (mL) by Race (Full Analysis Set)
Race: Asian

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	736.98 (1796.60)						
	Placebo (N=74)	23 (31.08%)	678.76 (1007.23)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	18 (25.35%)	-107.83 (277.21)	-46.64 (35.52)	(-118.98, 25.70)	-90.56 (-151.47, -29.65)	0.005	-0.59 (-1.26 ,0.07)	0.525
	Placebo (N=74)	21 (28.38%)	-12.69 (76.70)	43.92 (32.38)	(-22.04, 109.88)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-100.77 (258.66)	-50.37 (25.72)	(-101.35, 0.61)	-80.64 (-123.90, -37.38)	<0.001	-0.70 (-1.35 ,-0.06)	0.142
	Placebo (N=74)	22 (29.73%)	1.38 (90.02)	30.27 (23.50)	(-16.31, 76.85)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.8.1.3 Change from Baseline in Target PN Volume (mL) by Race (Full Analysis Set)
Race: White

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	38 (53.52%)	283.69 (598.70)					
	Placebo (N=74)	43 (58.11%)	480.56 (945.54)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	24 (33.80%)	-18.92 (130.18)	-23.43 (22.88)	(-69.48, 22.61)	-44.78 (-101.30, 11.74)	0.118	
	Placebo (N=74)	27 (36.49%)	19.63 (69.80)	21.35 (19.47)	(-17.84, 60.53)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	35 (49.30%)	-20.36 (96.98)	-23.04 (10.38)	(-43.52, -2.56)	-42.81 (-68.34, -17.27)	0.001	-0.71 (-1.18 ,-0.23)
	Placebo (N=74)	41 (55.41%)	17.26 (83.05)	19.77 (9.14)	(1.73, 37.81)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.8.1.3 Change from Baseline in Target PN Volume (mL) by Race (Full Analysis Set)
Race: Other

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	345.35 (541.77)					
	Placebo (N=74)	5 (6.76%)	317.18 (370.84)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	4 (5.63%)	-77.82 (157.94)	-255.98 (13.27)	(-298.21, -213.76)	24.66 (-6.99, 56.31)	0.089	
	Placebo (N=74)	4 (5.41%)	14.40 (37.43)	-280.64 (19.58)	(-342.94, -218.34)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	4 (5.63%)	-63.93 (119.97)	-111.79 (20.89)	(-156.32, -67.26)	-29.30 (-75.33, 16.72)	0.195	
	Placebo (N=74)	5 (6.76%)	-13.06 (65.25)	-82.49 (28.40)	(-143.02, -21.96)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
Program: t_pn_continuous_subgroup.sas Executed: 30SEP2025 10:52:14

1.1.1.2 Volumenänderung der Zielläsion – Prozentuale Volumenänderung der Zielläsion im Vergleich zu Baseline – Zyklus 12, Tag 28 und über die randomisierte Phase

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Table 7.7.1.1 Percent Change from Baseline in Target PN Volume (mL) by Age Group (Full Analysis Set)
Age Group: 18 - <30

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	32 (45.07%)	140.28 (146.87)						
	Placebo (N=74)	42 (56.76%)	499.71 (746.03)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	23 (32.39%)	-7.40 (18.13)	-8.66 (3.29)	(-15.27, -2.06)	-11.35 (-19.36, -3.34)	0.006	-0.74 (-1.30 ,-0.17)	0.623
	Placebo (N=74)	33 (44.59%)	2.60 (11.11)	2.69 (2.57)	(-2.48, 7.85)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-7.00 (14.95)	-7.87 (1.62)	(-11.08, -4.67)	-11.37 (-15.19, -7.55)	<0.001	-1.35 (-1.89 ,-0.81)	0.461
	Placebo (N=74)	41 (55.41%)	3.92 (10.82)	3.50 (1.27)	(0.99, 6.01)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.1 Percent Change from Baseline in Target PN Volume (mL) by Age Group (Full Analysis Set)
Age Group: 30 - <65

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	39 (54.93%)	760.40 (1611.16)					
	Placebo (N=74)	32 (43.24%)	591.79 (1132.94)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-11.09 (26.22)	-13.59 (4.93)	(-23.56, -3.63)	-7.68 (-21.39, 6.02)	0.264	
	Placebo (N=74)	20 (27.03%)	-2.55 (14.44)	-5.91 (5.87)	(-17.77, 5.95)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	37 (52.11%)	-9.90 (18.62)	-11.72 (1.98)	(-15.63, -7.81)	-8.80 (-14.00, -3.61)	0.001	-0.71 (-1.21 ,-0.20)
	Placebo (N=74)	30 (40.54%)	-0.06 (14.35)	-2.92 (2.31)	(-7.48, 1.64)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.2 Percent Change from Baseline in Target PN Volume (mL) by Sex (Full Analysis Set)
Sex: Male

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	33 (46.48%)	601.79 (1509.24)						
	Placebo (N=74)	42 (56.76%)	625.19 (879.40)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	26 (36.62%)	-8.66 (26.31)	-10.46 (4.46)	(-19.42, -1.50)	-5.61 (-16.55, 5.33)	0.308		0.208
	Placebo (N=74)	29 (39.19%)	-1.43 (13.16)	-4.85 (4.33)	(-13.55, 3.84)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	31 (43.66%)	-7.95 (20.13)	-9.31 (2.01)	(-13.28, -5.34)	-7.00 (-11.75, -2.25)	0.004	-0.59 (-1.08 ,-0.10)	0.020
	Placebo (N=74)	40 (54.05%)	0.70 (13.03)	-2.31 (1.91)	(-6.08, 1.46)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.2 Percent Change from Baseline in Target PN Volume (mL) by Sex (Full Analysis Set)
Sex: Female

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	38 (53.52%)	375.93 (934.03)					
	Placebo (N=74)	32 (43.24%)	427.09 (989.35)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	25 (35.21%)	-10.22 (18.95)	-11.80 (3.71)	(-19.29, -4.30)	-14.31 (-24.15, -4.46)	0.005	-0.79 (-1.39 ,-0.19)
	Placebo (N=74)	24 (32.43%)	3.18 (11.64)	2.51 (3.44)	(-4.44, 9.46)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	34 (47.89%)	-9.30 (13.49)	-10.65 (1.58)	(-13.77, -7.53)	-14.14 (-18.11, -10.17)	<0.001	-1.61 (-2.18 ,-1.04)
	Placebo (N=74)	31 (41.89%)	4.29 (11.52)	3.49 (1.45)	(0.63, 6.35)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.3 Percent Change from Baseline in Target PN Volume (mL) by Race (Full Analysis Set)
Race: Asian

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	736.98 (1796.60)						
	Placebo (N=74)	23 (31.08%)	678.76 (1007.23)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	18 (25.35%)	-22.24 (15.09)	-23.53 (5.35)	(-34.44, -12.63)	-25.37 (-34.55, -16.19)	<0.001	-1.10 (-1.80 ,-0.40)	0.011
	Placebo (N=74)	21 (28.38%)	2.28 (11.12)	1.83 (4.88)	(-8.11, 11.78)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-17.07 (14.64)	-18.98 (2.65)	(-24.23, -13.72)	-20.62 (-25.08, -16.16)	<0.001	-1.74 (-2.48 ,-1.01)	0.000
	Placebo (N=74)	22 (29.73%)	2.55 (8.74)	1.64 (2.42)	(-3.16, 6.44)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.7.1.3 Percent Change from Baseline in Target PN Volume (mL) by Race (Full Analysis Set)
Race: White

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	38 (53.52%)	283.69 (598.70)					
	Placebo (N=74)	43 (58.11%)	480.56 (945.54)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	24 (33.80%)	-1.17 (26.49)	-0.90 (5.00)	(-10.95, 9.16)	-0.80 (-13.15, 11.54)	0.896	
	Placebo (N=74)	27 (36.49%)	-0.14 (13.45)	-0.09 (4.25)	(-8.65, 8.47)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	35 (49.30%)	-4.34 (18.17)	-4.71 (1.89)	(-8.44, -0.99)	-6.76 (-11.40, -2.12)	0.005	-0.61 (-1.08 ,-0.15)
	Placebo (N=74)	41 (55.41%)	2.74 (13.23)	2.05 (1.66)	(-1.23, 5.33)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.7.1.3 Percent Change from Baseline in Target PN Volume (mL) by Race (Full Analysis Set)
Race: Other

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	345.35 (541.77)					
	Placebo (N=74)	5 (6.76%)	317.18 (370.84)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	4 (5.63%)	-1.95 (16.88)	-54.93 (12.51)	(-94.76, -15.11)	34.52 (4.67, 64.37)	0.035	0.95 (-0.90 ,2.81)
	Placebo (N=74)	4 (5.41%)	-1.89 (17.89)	-89.46 (18.46)	(-148.22, -30.69)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	4 (5.63%)	-6.12 (12.98)	-19.74 (6.27)	(-33.11, -6.37)	10.01 (-3.80, 23.83)	0.143	
	Placebo (N=74)	5 (6.76%)	-4.46 (12.85)	-29.76 (8.53)	(-47.93, -11.58)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.7.1.4 Percent Change from Baseline in Target PN Volume (mL) by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	532.88 (778.20)						
	Placebo (N=74)	9 (12.16%)	836.02 (1825.10)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	2 (2.82%)	-32.67 (25.29)	-34.86 (6.89)	(-56.78, -12.93)	-17.13 (-44.25, 10.00)	0.138		0.132
	Placebo (N=74)	6 (8.11%)	0.70 (5.99)	-17.73 (6.64)	(-38.85, 3.39)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	-15.90 (13.54)	-24.30 (3.10)	(-30.70, -17.90)	-15.62 (-22.69, -8.55)	<0.001	-1.47 (-2.84 ,-0.09)	0.254
	Placebo (N=74)	9 (12.16%)	1.59 (5.91)	-8.68 (3.73)	(-16.38, -0.97)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subjects with missing ethnicity are excluded.
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Table 7.7.1.4 Percent Change from Baseline in Target PN Volume (mL) by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	63 (88.73%)	498.72 (1288.77)					
	Placebo (N=74)	63 (85.14%)	507.39 (751.40)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	46 (64.79%)	-9.40 (22.80)	-11.31 (2.97)	(-17.21, -5.42)	-10.93 (-18.68, -3.18)	0.006	-0.55 (-0.97 ,-0.12)
	Placebo (N=74)	45 (60.81%)	0.79 (12.76)	-0.38 (2.90)	(-6.15, 5.38)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	57 (80.28%)	-8.48 (17.50)	-10.14 (1.36)	(-12.83, -7.46)	-11.36 (-14.78, -7.94)	<0.001	-1.11 (-1.51 ,-0.72)
	Placebo (N=74)	60 (81.08%)	2.67 (12.92)	1.22 (1.29)	(-1.32, 3.75)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subjects with missing ethnicity are excluded.
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Table 7.7.1.5 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: North America

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	761.61 (2053.25)						
	Placebo (N=74)	6 (8.11%)	307.86 (660.80)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	-8.79 (17.38)	-9.73 (8.60)	(-30.77, 11.31)	-14.47 (-45.01, 16.07)	0.290		0.040
	Placebo (N=74)	5 (6.76%)	4.11 (16.10)	4.75 (8.89)	(-17.00, 26.49)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	-8.99 (13.14)	-9.76 (3.25)	(-16.41, -3.11)	-11.13 (-20.45, -1.81)	0.021	-1.14 (-2.37 ,0.10)	0.005
	Placebo (N=74)	6 (8.11%)	2.09 (11.45)	1.37 (3.39)	(-5.56, 8.29)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.5 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Europe

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	456.99 (1094.74)					
	Placebo (N=74)	27 (36.49%)	534.21 (861.21)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	19 (26.76%)	-0.51 (29.09)	-2.16 (6.27)	(-14.92, 10.61)	1.12 (-16.01, 18.26)	0.895	
	Placebo (N=74)	17 (22.97%)	-2.59 (16.23)	-3.28 (6.14)	(-15.79, 9.23)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	25 (35.21%)	-3.74 (19.45)	-4.96 (2.50)	(-9.90, -0.02)	-4.92 (-11.27, 1.44)	0.128	
	Placebo (N=74)	26 (35.14%)	1.47 (16.03)	-0.04 (2.41)	(-4.81, 4.73)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.5 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Asia

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	18 (25.35%)	525.83 (1451.26)					
	Placebo (N=74)	21 (28.38%)	549.80 (722.09)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	-22.11 (15.48)	-21.53 (3.60)	(-28.88, -14.19)	-23.45 (-32.65, -14.25)	<0.001	-1.60 (-2.39 ,-0.80)
	Placebo (N=74)	19 (25.68%)	1.44 (9.73)	1.92 (3.28)	(-4.79, 8.62)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	-16.85 (15.37)	-16.69 (1.87)	(-20.41, -12.98)	-19.05 (-23.69, -14.41)	<0.001	-2.44 (-3.33 ,-1.55)
	Placebo (N=74)	20 (27.03%)	2.01 (7.99)	2.36 (1.70)	(-1.01, 5.72)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.5 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	322.73 (511.92)					
	Placebo (N=74)	20 (27.03%)	605.42 (1266.07)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-6.67 (13.26)	-3.62 (4.30)	(-12.65, 5.41)	-9.58 (-20.17, 1.01)	0.073	
	Placebo (N=74)	12 (16.22%)	2.59 (9.49)	5.96 (4.16)	(-2.77, 14.69)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	14 (19.72%)	-6.31 (13.04)	-3.23 (2.68)	(-8.57, 2.11)	-10.53 (-16.09, -4.98)	<0.001	-1.00 (-1.77 ,-0.24)
	Placebo (N=74)	19 (25.68%)	3.94 (11.88)	7.30 (2.38)	(2.55, 12.05)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.6 Percent Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	13 (18.31%)	393.80 (830.95)						
	Placebo (N=74)	18 (24.32%)	890.51 (1355.95)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	10 (14.08%)	3.83 (38.29)	2.76 (22.61)	(-46.50, 52.02)	3.22 (-34.60, 41.03)	0.856		0.203
	Placebo (N=74)	9 (12.16%)	2.45 (12.92)	-0.46 (16.72)	(-36.89, 35.97)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-1.77 (26.99)	-6.94 (6.68)	(-20.31, 6.43)	-5.85 (-17.19, 5.49)	0.306		0.011
	Placebo (N=74)	17 (22.97%)	4.36 (16.05)	-1.09 (5.19)	(-11.47, 9.29)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.7.1.6 Percent Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	255.95 (526.11)					
	Placebo (N=74)	12 (16.22%)	325.80 (362.53)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	-9.02 (18.17)	-11.17 (6.57)	(-25.38, 3.03)	-10.55 (-28.19, 7.08)	0.219	
	Placebo (N=74)	11 (14.86%)	1.15 (12.60)	-0.62 (5.48)	(-12.45, 11.21)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	-9.98 (12.20)	-12.67 (2.88)	(-18.46, -6.89)	-13.79 (-20.71, -6.87)	<0.001	-1.46 (-2.42 ,-0.50)
	Placebo (N=74)	12 (16.22%)	4.52 (14.09)	1.11 (2.36)	(-3.63, 5.85)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.7.1.6 Percent Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	1311.29 (2283.34)					
	Placebo (N=74)	11 (14.86%)	781.94 (902.99)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	-19.67 (17.38)	-14.88 (5.14)	(-25.90, -3.86)	-25.44 (-39.86, -11.03)	0.002	-1.33 (-2.35 ,-0.30)
	Placebo (N=74)	9 (12.16%)	4.95 (10.11)	10.56 (6.39)	(-3.14, 24.27)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	15 (21.13%)	-14.92 (14.84)	-12.63 (2.08)	(-16.79, -8.47)	-21.54 (-27.29, -15.79)	<0.001	-2.47 (-3.57 ,-1.38)
	Placebo (N=74)	11 (14.86%)	4.66 (8.60)	8.91 (2.70)	(3.51, 14.32)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.7.1.6 Percent Change from Baseline in Target PN Volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	30 (42.25%)	165.77 (250.37)					
	Placebo (N=74)	32 (43.24%)	304.04 (706.53)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-10.09 (14.11)	-10.75 (3.66)	(-18.18, -3.32)	-8.13 (-17.47, 1.21)	0.086	
	Placebo (N=74)	23 (31.08%)	-1.85 (13.74)	-2.62 (3.46)	(-9.64, 4.40)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	-7.49 (12.99)	-8.15 (1.59)	(-11.30, -5.00)	-7.15 (-11.02, -3.29)	<0.001	-0.85 (-1.40 ,-0.29)
	Placebo (N=74)	30 (40.54%)	-0.14 (10.55)	-1.00 (1.53)	(-4.02, 2.03)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.7.1.7 Percent Change from Baseline in Target PN Volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	29 (40.85%)	22.55 (16.26)						
	Placebo (N=74)	19 (25.68%)	28.32 (12.71)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	21 (29.58%)	-8.80 (15.04)	-10.79 (4.41)	(-19.83, -1.74)	-4.93 (-16.51, 6.65)	0.390		0.873
	Placebo (N=74)	13 (17.57%)	-1.36 (16.69)	-5.85 (5.25)	(-16.63, 4.93)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	-8.90 (11.89)	-10.19 (1.87)	(-13.89, -6.48)	-8.12 (-12.77, -3.47)	<0.001	-0.83 (-1.48 ,-0.18)	0.688
	Placebo (N=74)	17 (22.97%)	1.44 (12.34)	-2.07 (2.27)	(-6.57, 2.44)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.7 Percent Change from Baseline in Target PN Volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	24 (33.80%)	145.73 (74.28)					
	Placebo (N=74)	25 (33.78%)	165.03 (89.91)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-9.97 (28.83)	-11.05 (7.31)	(-25.93, 3.82)	-11.33 (-26.81, 4.15)	0.146	
	Placebo (N=74)	20 (27.03%)	0.26 (12.77)	0.28 (6.45)	(-12.85, 13.41)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	-9.21 (22.06)	-9.96 (3.27)	(-16.44, -3.48)	-12.00 (-18.55, -5.45)	<0.001	-0.80 (-1.42 ,-0.19)
	Placebo (N=74)	25 (33.78%)	2.38 (12.64)	2.04 (2.81)	(-3.52, 7.61)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.7 Percent Change from Baseline in Target PN Volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	18 (25.35%)	1666.29 (2055.91)					
	Placebo (N=74)	30 (40.54%)	1175.38 (1202.95)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	10 (14.08%)	-9.67 (25.01)	-9.86 (5.49)	(-21.23, 1.50)	-9.16 (-21.58, 3.26)	0.141	
	Placebo (N=74)	20 (27.03%)	2.37 (9.42)	-0.70 (3.78)	(-8.52, 7.12)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	-7.31 (17.08)	-8.76 (2.30)	(-13.31, -4.21)	-9.31 (-14.88, -3.73)	0.001	-1.00 (-1.67 ,-0.34)
	Placebo (N=74)	29 (39.19%)	2.81 (12.53)	0.55 (1.69)	(-2.80, 3.89)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3), and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.8 Percent Change from Baseline in Target PN Volume (mL) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	21 (29.58%)	642.17 (1114.51)						
	Placebo (N=74)	21 (28.38%)	667.47 (744.42)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	13 (18.31%)	-12.10 (17.81)	-13.34 (4.38)	(-22.40, -4.28)	-12.75 (-24.66, -0.85)	0.037	-0.78 (-1.57 ,0.02)	0.738
	Placebo (N=74)	16 (21.62%)	0.37 (12.02)	-0.59 (4.02)	(-8.91, 7.74)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	-10.80 (12.99)	-12.03 (2.10)	(-16.21, -7.85)	-13.43 (-18.67, -8.20)	<0.001	-1.52 (-2.28 ,-0.77)	0.343
	Placebo (N=74)	21 (28.38%)	2.69 (13.14)	1.40 (1.88)	(-2.33, 5.14)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.8 Percent Change from Baseline in Target PN Volume (mL) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	50 (70.42%)	413.18 (1281.36)					
	Placebo (N=74)	53 (71.62%)	488.84 (992.28)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	38 (53.52%)	-8.51 (24.40)	-10.10 (3.35)	(-16.78, -3.42)	-9.99 (-18.92, -1.06)	0.029	-0.49 (-0.96 ,-0.02)
	Placebo (N=74)	37 (50.00%)	0.78 (12.99)	-0.11 (3.25)	(-6.60, 6.38)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	48 (67.61%)	-7.85 (18.35)	-9.48 (1.47)	(-12.37, -6.59)	-10.25 (-14.01, -6.48)	<0.001	-1.01 (-1.44 ,-0.58)
	Placebo (N=74)	50 (67.57%)	2.17 (12.22)	0.77 (1.41)	(-2.01, 3.54)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and geographical region as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.9 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

				Comparison of Treatment Groups					
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges'g) (95% CI) [e]	Interaction p-value [f]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	194.72 (271.17)						
	Placebo (N=74)	13 (17.57%)	452.40 (689.71)						
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	10 (14.08%)	-22.23 (15.56)	-18.34 (4.70)	(-28.26, -8.41)	-22.14 (-34.40, -9.89)	0.001	-1.41 (-2.44 ,-0.38)	0.035
	Placebo (N=74)	11 (14.86%)	-0.03 (11.27)	3.81 (4.59)	(-5.89, 13.50)				
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-15.67 (15.87)	-13.46 (2.54)	(-18.55, -8.36)	-17.02 (-23.43, -10.60)	<0.001	-1.94 (-3.00 ,-0.87)	0.002
	Placebo (N=74)	12 (16.22%)	1.83 (9.44)	3.56 (2.46)	(-1.36, 8.49)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.9 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	7 (9.86%)	1046.15 (2308.25)					
	Placebo (N=74)	8 (10.81%)	708.08 (792.49)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	6 (8.45%)	-21.90 (16.83)	-23.55 (5.12)	(-34.96, -12.14)	-24.22 (-39.14, -9.30)	0.005	-1.74 (-3.14 ,-0.34)
	Placebo (N=74)	8 (10.81%)	3.45 (7.34)	0.67 (4.73)	(-9.86, 11.20)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	6 (8.45%)	-18.86 (14.70)	-19.85 (2.66)	(-25.27, -14.43)	-21.05 (-28.14, -13.96)	<0.001	-2.91 (-4.65 ,-1.17)
	Placebo (N=74)	8 (10.81%)	2.26 (5.51)	1.20 (2.46)	(-3.80, 6.20)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.9 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	31 (43.66%)	448.70 (1039.33)					
	Placebo (N=74)	30 (40.54%)	505.37 (824.75)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	-0.20 (27.77)	-2.23 (5.64)	(-13.66, 9.20)	0.38 (-14.43, 15.19)	0.959	
	Placebo (N=74)	20 (27.03%)	-1.53 (15.30)	-2.61 (5.48)	(-13.71, 8.49)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-2.77 (19.52)	-4.41 (2.35)	(-9.06, 0.23)	-4.56 (-10.37, 1.25)	0.123	
	Placebo (N=74)	29 (39.19%)	1.90 (15.18)	0.15 (2.27)	(-4.34, 4.63)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.7.1.9 Percent Change from Baseline in Target PN Volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

				Comparison of Treatment Groups				
Visit	Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Means (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Baseline	Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	489.54 (1341.46)					
	Placebo (N=74)	23 (31.08%)	574.71 (1216.23)					
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID (N=71)	13 (18.31%)	-9.43 (12.02)	-9.65 (3.53)	(-16.94, -2.36)	-13.09 (-23.26, -2.91)	0.014	-0.99 (-1.83 ,-0.15)
	Placebo (N=74)	14 (18.92%)	2.72 (12.16)	3.44 (3.46)	(-3.71, 10.59)			
Over Randomized Period	Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-9.33 (10.51)	-9.78 (1.87)	(-13.49, -6.06)	-12.83 (-17.49, -8.17)	<0.001	-1.55 (-2.27 ,-0.84)
	Placebo (N=74)	22 (29.73%)	3.21 (12.41)	3.05 (1.67)	(-0.27, 6.37)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
LS Mean Change and Between-Group Differences were estimated using a linear fixed-effects model with Kenward-Roger degrees of freedom.
For individual visits, the model included baseline target PN volume, treatment group and PAINS-pNF chronic target PN pain intensity group (<3, >=3) as fixed effects. For the overall randomized period, the model additionally included visit, baseline target PN volume*visit, and treatment group*visit interactions.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value is derived from Difference in LS Means using above model.
[e] SMD is calculated using Hedges' g method with bias correction when p-value is < 0.05.
[f] p-value for interaction between treatment and subgroup factors using above model including interaction for treatment and subgroup.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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1.1.1.3 Volumenänderung der Zielläsion – Beste erreichte prozentuale Volumenänderung der Zielläsion

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Table 7.5.1.1: Best percent change from baseline in target PN volume (mL) by Age Group (Full Analysis Set)
Age Group: 18 - <30

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-11.90 (13.20)	-12.59 (2.49)	(-17.56, -7.62)	-11.29 (-17.20, -5.39)	<0.001	-0.87 (-1.38, -0.36)	0.635
Placebo (N=74)	41 (55.41%)	-0.78 (10.49)	-1.30 (1.98)	(-5.26, 2.67)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.1: Best percent change from baseline in target PN volume (mL) by Age Group (Full Analysis Set)
Age Group: 30 - <65

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	37 (52.11%)	-15.71 (14.50)	-17.37 (2.67)	(-22.72, -12.02)	-8.83 (-15.67, -1.99)	0.012	-0.53 (-1.03, -0.03)
Placebo (N=74)	30 (40.54%)	-6.15 (12.35)	-8.54 (3.04)	(-14.63, -2.46)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.2: Best percent change from baseline in target PN volume (mL) by Sex (Full Analysis Set)
Sex: Male

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	31 (43.66%)	-14.11 (14.84)	-14.57 (2.69)	(-19.94, -9.20)	-8.11 (-14.39, -1.83)	0.012	-0.52 (-1.01, -0.04)	0.163
Placebo (N=74)	40 (54.05%)	-4.94 (11.23)	-6.46 (2.48)	(-11.42, -1.50)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.2: Best percent change from baseline in target PN volume (mL) by Sex (Full Analysis Set)
Sex: Female

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	34 (47.89%)	-14.03 (13.37)	-15.84 (2.60)	(-21.04, -10.63)	-14.38 (-20.95, -7.81)	<0.001	-0.98 (-1.51, -0.46)
Placebo (N=74)	31 (41.89%)	-0.61 (11.66)	-1.46 (2.44)	(-6.34, 3.43)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.3: Best percent change from baseline in target PN volume (mL) by Race (Full Analysis Set)
Race: Asian

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-22.11 (14.17)	-23.31 (4.33)	(-32.10, -14.51)	-20.05 (-27.46, -12.64)	<0.001	-1.04 (-1.70, -0.37)	0.030
Placebo (N=74)	22 (29.73%)	-2.67 (6.44)	-3.26 (3.98)	(-11.34, 4.82)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.5.1.3: Best percent change from baseline in target PN volume (mL) by Race (Full Analysis Set)
Race: White

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	35 (49.30%)	-10.35 (13.47)	-10.65 (2.39)	(-15.42, -5.87)	-7.33 (-13.34, -1.32)	0.018	-0.52 (-0.98, -0.05)
Placebo (N=74)	41 (55.41%)	-3.01 (12.01)	-3.32 (2.16)	(-7.63, 1.00)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.5.1.3: Best percent change from baseline in target PN volume (mL) by Race (Full Analysis Set)
Race: Other

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	4 (5.63%)	-13.92 (7.67)	-22.81 (5.64)	(-38.47, -7.14)	6.83 (-11.19, 24.84)	0.352	
Placebo (N=74)	5 (6.76%)	-10.82 (11.75)	-29.63 (7.25)	(-49.76, -9.50)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 7.5.1.4: Best percent change from baseline in target PN volume (mL) by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	5 (7.04%)	-21.53 (16.56)	-31.83 (1.96)	(-36.26, -27.41)	-12.43 (-17.44, -7.43)	<0.001	-1.67 (-3.06, -0.27)	0.275
Placebo (N=74)	9 (12.16%)	-2.43 (2.91)	-19.40 (2.66)	(-25.41, -13.40)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subjects with missing ethnicity are excluded.
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Table 7.5.1.4: Best percent change from baseline in target PN volume (mL) by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	57 (80.28%)	-13.61 (14.05)	-14.99 (1.95)	(-18.85, -11.12)	-10.83 (-15.66, -5.99)	<0.001	-0.74 (-1.12, -0.37)
Placebo (N=74)	60 (81.08%)	-2.89 (12.22)	-4.16 (1.83)	(-7.79, -0.53)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subjects with missing ethnicity are excluded.
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Table 7.5.1.5: Best percent change from baseline in target PN volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: North America

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	9 (12.68%)	-14.59 (10.85)	-14.57 (3.88)	(-23.10, -6.04)	-8.47 (-21.59, 4.64)	0.183		0.141
Placebo (N=74)	6 (8.11%)	-5.61 (9.83)	-6.09 (4.72)	(-16.48, 4.29)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.5: Best percent change from baseline in target PN volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Europe

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	25 (35.21%)	-10.42 (14.08)	-11.44 (3.26)	(-17.99, -4.89)	-6.13 (-14.29, 2.03)	0.137	
Placebo (N=74)	26 (35.14%)	-4.36 (14.40)	-5.31 (3.15)	(-11.64, 1.02)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.5: Best percent change from baseline in target PN volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Asia

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	-21.97 (14.97)	-21.87 (3.06)	(-28.10, -15.64)	-18.78 (-26.51, -11.04)	<0.001	-1.48 (-2.24, -0.73)
Placebo (N=74)	20 (27.03%)	-3.17 (5.74)	-3.09 (2.73)	(-8.66, 2.48)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.5: Best percent change from baseline in target PN volume (mL) by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	14 (19.72%)	-10.63 (11.29)	-6.79 (3.80)	(-14.57, 0.98)	-10.76 (-19.48, -2.03)	0.017	-0.70 (-1.44, 0.04)
Placebo (N=74)	19 (25.68%)	-0.32 (12.48)	3.96 (3.53)	(-3.28, 11.20)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.6: Best percent change from baseline in target PN volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-12.63 (20.90)	-18.53 (9.03)	(-37.32, 0.25)	-12.69 (-28.13, 2.76)	0.102		0.196
Placebo (N=74)	17 (22.97%)	-0.81 (13.55)	-5.85 (7.00)	(-20.41, 8.72)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.5.1.6: Best percent change from baseline in target PN volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	12 (16.90%)	-13.08 (11.48)	-15.36 (5.17)	(-26.26, -4.46)	-11.07 (-24.05, 1.92)	0.090	
Placebo (N=74)	12 (16.22%)	-1.02 (14.98)	-4.30 (4.44)	(-13.66, 5.07)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.5.1.6: Best percent change from baseline in target PN volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	15 (21.13%)	-19.55 (14.34)	-18.48 (3.26)	(-25.31, -11.65)	-20.47 (-29.92, -11.02)	<0.001	-1.50 (-2.43, -0.58)
Placebo (N=74)	11 (14.86%)	-0.37 (6.48)	1.99 (4.20)	(-6.80, 10.78)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.5.1.6: Best percent change from baseline in target PN volume (mL) by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	-12.04 (11.12)	-12.02 (2.44)	(-16.93, -7.12)	-5.86 (-11.79, 0.07)	0.053	
Placebo (N=74)	30 (40.54%)	-5.86 (10.15)	-6.16 (2.40)	(-10.98, -1.35)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
Subject with target PN location 'Other' is excluded.
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Table 7.5.1.7: Best percent change from baseline in target PN volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	27 (38.03%)	-13.31 (10.21)	-13.99 (3.23)	(-20.52, -7.45)	-8.35 (-16.34, -0.35)	0.041	-0.49 (-1.13, 0.14)	0.485
Placebo (N=74)	17 (22.97%)	-3.49 (14.29)	-5.64 (3.95)	(-13.64, 2.36)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.7: Best percent change from baseline in target PN volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	22 (30.99%)	-16.38 (16.28)	-16.70 (4.43)	(-25.66, -7.75)	-14.27 (-23.18, -5.35)	0.002	-0.70 (-1.31, -0.09)
Placebo (N=74)	25 (33.78%)	-2.34 (12.22)	-2.44 (3.87)	(-10.26, 5.39)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.7: Best percent change from baseline in target PN volume (mL) by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	16 (22.54%)	-12.15 (16.41)	-13.29 (3.15)	(-19.66, -6.92)	-8.11 (-15.94, -0.28)	0.043	-0.63 (-1.27, 0.01)
Placebo (N=74)	29 (39.19%)	-3.40 (9.35)	-5.18 (2.34)	(-9.92, -0.44)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) and geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.8: Best percent change from baseline in target PN volume (mL) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	17 (23.94%)	-14.37 (13.13)	-15.90 (3.47)	(-22.97, -8.82)	-11.05 (-19.87, -2.23)	0.016	-0.76 (-1.44, -0.07)	0.930
Placebo (N=74)	21 (28.38%)	-3.16 (12.92)	-4.85 (3.13)	(-11.22, 1.53)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.8: Best percent change from baseline in target PN volume (mL) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	48 (67.61%)	-13.96 (14.40)	-15.14 (2.00)	(-19.11, -11.16)	-10.94 (-16.03, -5.85)	<0.001	-0.79 (-1.21, -0.37)
Placebo (N=74)	50 (67.57%)	-3.00 (11.05)	-4.20 (1.93)	(-8.03, -0.37)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, geographical region as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.9: Best percent change from baseline in target PN volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

			Comparison of treatment groups					
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]	Interaction p-value [f]
Selumetinib 25 mg/m2 BID (N=71)	11 (15.49%)	-21.19 (14.77)	-19.04 (3.85)	(-27.10, -10.99)	-17.20 (-27.48, -6.92)	0.002	-1.30 (-2.26, -0.35)	0.108
Placebo (N=74)	12 (16.22%)	-3.93 (6.63)	-1.84 (3.67)	(-9.53, 5.85)				

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
[f] Interaction p-value tests whether the treatment effect differs across levels of the subgroup (Type III F-test for the treatment-by-subgroup interaction in the ANCOVA model).
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.9: Best percent change from baseline in target PN volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	6 (8.45%)	-23.40 (16.64)	-24.59 (4.94)	(-35.59, -13.59)	-20.90 (-35.28, -6.52)	0.009	-1.56 (-2.90, -0.22)
Placebo (N=74)	8 (10.81%)	-2.02 (4.24)	-3.69 (4.55)	(-13.84, 6.46)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.9: Best percent change from baseline in target PN volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	28 (39.44%)	-9.32 (14.94)	-10.73 (3.19)	(-17.12, -4.33)	-5.86 (-13.63, 1.90)	0.136	
Placebo (N=74)	29 (39.19%)	-3.54 (13.93)	-4.87 (3.09)	(-11.07, 1.33)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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Table 7.5.1.9: Best percent change from baseline in target PN volume (mL) by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

			Comparison of treatment groups				
Treatment Group	n (%)	Mean (SD)	LS Mean Change (SE) [a]	(95% CI) [b]	Difference in LS Mean (95% CI) [c]	p-value [d]	SMD (Hedges' g) (95% CI) [e]
Selumetinib 25 mg/m2 BID (N=71)	20 (28.17%)	-13.99 (7.96)	-13.71 (2.42)	(-18.60, -8.82)	-11.71 (-18.40, -5.02)	0.001	-1.06 (-1.73, -0.40)
Placebo (N=74)	22 (29.73%)	-2.29 (12.42)	-2.00 (2.30)	(-6.66, 2.65)			

LS = Least Squares; CI = Confidence Interval; SMD = Standardized Mean Difference
Analysis of covariance (ANCOVA) models overall best percentage change from baseline as the response, with baseline target PN volume as a covariate, and treatment group, PAINS-pNF chronic target PN pain intensity group (<3, >=3) as factors.
[a] LS Mean Change is the model-estimated mean percent change from baseline within each treatment group.
[b] 95% CI for LS Mean Change.
[c] Difference in LS Mean is the model-estimated between-group contrast.
[d] p-value corresponds to the LS Mean contrast from the above ANCOVA model.
[e] SMD is calculated using Hedges' g with bias correction when p-value is < 0.05.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with result available.
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1.1.1.4 Volumenänderung der Zielläsion – Patienten mit einer Verringerung der Zielläsion um ≥ 20 % – Zyklus 12, Tag 28

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Table 7.1.1.1: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Age Group (Full Analysis Set)
Age Group: 18 - <30

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]	Interaction p-value [c]
Selumetinib 25 mg/m2 BID N=71	23	6 (26.09)	NC	NC	0.26 (0.08, 0.44)	0.003	1.000
Placebo N=74	33	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
[c] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 7.1.1.1: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Age Group (Full Analysis Set)
Age Group: 30 - <65

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	28	8 (28.57)	3.60 (0.67, 19.22)	2.86 (0.68, 12.05)	0.19 (-0.03, 0.40)	0.160
Placebo N=74	20	2 (10.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 7.1.1.2: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Male

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]	Interaction p-value [c]
Selumetinib 25 mg/m2 BID N=71	26	9 (34.62)	14.82 (1.72, 127.52)	10.04 (1.36, 73.95)	0.31 (0.12, 0.51)	0.004	0.615
Placebo N=74	29	1 (3.45)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
[c] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 7.1.1.2: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Female

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	25	5 (20.00)	5.75 (0.62, 53.43)	4.80 (0.60, 38.14)	0.16 (-0.02, 0.33)	0.189
Placebo N=74	24	1 (4.17)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 7.1.1.3: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Asian

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]	Interaction p-value [c]
Selumetinib 25 mg/m2 BID N=71	18	11 (61.11)	NC	NC	0.61 (0.39, 0.84)	<0.001	0.894
Placebo N=74	21	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
[c] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 7.1.1.3: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: White

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	24	2 (8.33)	2.36 (0.20, 27.85)	2.25 (0.22, 23.28)	0.05 (-0.09, 0.18)	0.595
Placebo N=74	27	1 (3.70)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 7.1.1.3: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Other

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	1.00 (0.04, 24.55)	1.00 (0.09, 11.03)	0.00 (-0.60, 0.60)	1.000
Placebo N=74	4	1 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 7.1.1.5: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)
Geographical Region: North America

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]	Interaction p-value [c]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	NC	NC	0.20 (-0.15, 0.55)	1.000	1.000
Placebo N=74	5	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
[c] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 7.1.1.5: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	19	3 (15.79)	1.41 (0.21, 9.62)	1.34 (0.25, 7.10)	0.04 (-0.18, 0.26)	1.000
Placebo N=74	17	2 (11.76)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 7.1.1.5: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	16	10 (62.50)	NC	NC	0.63 (0.39, 0.86)	<0.001
Placebo N=74	19	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 7.1.1.8: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]	Interaction p-value [c]
Selumetinib 25 mg/m2 BID N=71	13	4 (30.77)	NC	NC	0.31 (0.06, 0.56)	0.030	1.000
Placebo N=74	16	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
[c] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 7.1.1.8: Patients with 20% Reduction in Target PN Volume at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with Reduction Number (%)[a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	38	10 (26.32)	6.25 (1.27, 30.88)	4.87 (1.14, 20.74)	0.21 (0.05, 0.37)	0.025
Placebo N=74	37	2 (5.41)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
[a] Count and proportion of patients who had least a 20% reduction in target PN volume compared to baseline.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and Cycle 12, Day 28 measurement available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.2 Endpunkt Ansprechen

1.1.2.1 Ansprechen – Objektive Ansprechrate (ORR) – Zyklus 16, Tag 28

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Table 3.1.1.8: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

					Comparison between groups			
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]	Interaction p-value [e]
Selumetinib 25 mg/m2 BID N=71	21	3 (14.29)	14.29	(3.05, 36.34)	4.76	(-17.49, 27.26)	1.000	0.232
Placebo N=74	21	2 (9.52)	9.52	(1.17, 30.38)				

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
[e] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
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Table 3.1.1.8: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

					Comparison between groups		
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]
Selumetinib 25 mg/m2 BID N=71	50	11 (22.00)	22.00	(11.53, 35.96)	18.23	(5.95, 32.13)	0.007
Placebo N=74	53	2 (3.77)	3.77	(0.46, 12.98)			

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
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Table 3.1.1.1: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Age Group (Full Analysis Set)
Age Group: 18 - <30

					Comparison between groups			
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]	Interaction p-value [e]
Selumetinib 25 mg/m2 BID N=71	32	6 (18.75)	18.75	(7.21, 36.44)	18.75	(8.84, 35.44)	0.005	1.000
Placebo N=74	42	0	0.00	(0.00, 8.41)				

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
[e] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
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Table 3.1.1.1: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Age Group (Full Analysis Set)
Age Group: 30 - <65

					Comparison between groups		
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]
Selumetinib 25 mg/m2 BID N=71	39	8 (20.51)	20.51	(9.30, 36.46)	8.01	(-10.61, 25.54)	0.527
Placebo N=74	32	4 (12.50)	12.50	(3.51, 28.99)			

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
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Table 3.1.1.2: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Sex (Full Analysis Set)
Sex: Male

					Comparison between groups			
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]	Interaction p-value [e]
Selumetinib 25 mg/m2 BID N=71	33	9 (27.27)	27.27	(13.30, 45.52)	22.51	(6.73, 40.36)	0.008	0.361
Placebo N=74	42	2 (4.76)	4.76	(0.58, 16.16)				

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
[e] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
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Table 3.1.1.2: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Sex (Full Analysis Set)
Sex: Female

					Comparison between groups		
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]
Selumetinib 25 mg/m2 BID N=71	38	5 (13.16)	13.16	(4.41, 28.09)	6.91	(-8.94, 22.35)	0.442
Placebo N=74	32	2 (6.25)	6.25	(0.77, 20.81)			

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
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Table 3.1.1.3: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Race (Full Analysis Set)
Race: Asian

					Comparison between groups			
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]	Interaction p-value [e]
Selumetinib 25 mg/m2 BID N=71	22	10 (45.45)	45.45	(24.39, 67.79)	45.45	(26.75, 65.54)	<0.001	0.673
Placebo N=74	23	0	0.00	(0.00, 14.82)				

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
[e] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 3.1.1.3: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Race (Full Analysis Set)
Race: White

					Comparison between groups		
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]
Selumetinib 25 mg/m2 BID N=71	38	3 (7.89)	7.89	(1.66, 21.38)	3.24	(-8.86, 16.92)	0.661
Placebo N=74	43	2 (4.65)	4.65	(0.57, 15.81)			

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 3.1.1.3: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Race (Full Analysis Set)
Race: Other

					Comparison between groups		
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	20.00	(0.51, 71.64)	-20.00	(-67.03, 38.05)	1.000
Placebo N=74	5	2 (40.00)	40.00	(5.27, 85.34)			

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10).
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Table 3.1.1.4: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

					Comparison between groups			
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]	Interaction p-value [e]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	20.00	(0.51, 71.64)	20.00	(-15.80, 63.73)	0.357	1.000
Placebo N=74	9	0	0.00	(0.00, 33.63)				

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
[e] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
Subjects with missing ethnicity are excluded.
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Table 3.1.1.4: Objective response rate by end of Cycle 16, primary analysis, on-treatment MRI volumetric assessments period by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

					Comparison between groups		
Treatment group	n	Number (%) of subjects with response [a]	Response rate (%)	95% CI [b]	Difference in response rate (%)	95% CI for difference in response rate [c]	p-value [d]
Selumetinib 25 mg/m2 BID N=71	63	13 (20.63)	20.63	(11.47, 32.70)	15.87	(4.62, 28.18)	0.014
Placebo N=74	63	3 (4.76)	4.76	(0.99, 13.29)			

[a] Includes subjects with a confirmed complete response or confirmed partial response as determined by ICR as per the REiNS criteria.
[b] 2-sided exact 95% CI calculated using the Clopper Pearson method. [c] 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.
[d] 2-sided p-value calculated using Fisher's exact method (alpha=0.047) to test the hypotheses for the primary analysis: H0: ORR Selumetinib = ORR Placebo vs H1: ORR Selumetinib /= ORR Placebo.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in treatment group within subgroup factor.
Full Analysis Set consists of subjects randomised to study intervention in the study.
On-treatment MRI volumetric assessment period - from first dose until discontinuation or data cut-off (whichever occurs first), excluding data during prolonged study intervention interruption (>28 continuous days of no study intervention) or within 28 days of recommencement.
CI = Confidence interval; ICR = Independent Central Review; MRI = Magnetic resonance imaging; PN = Plexiform Neurofibroma.
REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
Subjects with missing ethnicity are excluded.
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1.1.3 Endpunkt Schmerz anhand PAINS-pNF

1.1.3.1 Schmerz anhand PAINS-pNF – chronischer Schmerz

1.1.3.1.1 Schmerz anhand PAINS-pNF – Zeit bis zur erstmaligen Verbesserung des chronischen Schmerzes um ≥ 1,5 Punkte – Hauptanalyse

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Table 14.11.1.5: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	9	5 (55.56)	4 (44.44)	3.71 (0.92, NC)	NC	(NC, NC)	0.035	0.808
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.5: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	26	14 (53.85)	12 (46.15)	7.36 (3.68, NC)	2.28	(0.94, 5.50)	0.079
	Placebo N=74	27	8 (29.63)	19 (70.37)	NC (7.39, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.5: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	17	8 (47.06)	9 (52.94)	NC (2.76, NC)	6.59	(1.26, 34.52)	0.234
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.5: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	16	11 (68.75)	5 (31.25)	6.44 (1.87, NC)	1.51	(0.57, 3.94)	0.196
	Placebo N=74	20	9 (45.00)	11 (55.00)	NC (1.84, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.6: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	6 (50.00)	NC (0.95, NC)	1.15	(0.35, 3.84)	0.670	0.053
	Placebo N=74	18	7 (38.89)	11 (61.11)	NC (1.84, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.11.1.6: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	6 (50.00)	NC (1.84, NC)	8.34	(0.75, 92.31)	0.020
	Placebo N=74	12	1 (8.33)	11 (91.67)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.11.1.6: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	16	9 (56.25)	7 (43.75)	3.68 (1.84, NC)	730	(12.43, NC)	0.012
	Placebo N=74	11	1 (9.09)	10 (90.91)	NC (7.39, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.11.1.6: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	28	17 (60.71)	11 (39.29)	6.44 (3.71, NC)	1.81	(0.87, 3.75)	0.221
	Placebo N=74	32	13 (40.63)	19 (59.38)	NC (5.52, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.11.1.7: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	28	20 (71.43)	8 (28.57)	3.68 (2.76, 7.36)	4.43	(1.61, 12.18)	0.007	0.168
	Placebo N=74	19	5 (26.32)	14 (73.68)	NC (6.44, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.7: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	23	14 (60.87)	9 (39.13)	6.44 (2.79, NC)	1.87	(0.79, 4.38)	0.120
	Placebo N=74	25	9 (36.00)	16 (64.00)	NC (6.44, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.7: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	17	4 (23.53)	13 (76.47)	NC (8.28, NC)	0.93	(0.27, 3.18)	0.835
	Placebo N=74	30	8 (26.67)	22 (73.33)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.8: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	20	6 (30.00)	14 (70.00)	NC (7.36, NC)	5.39	(0.59, 49.25)	0.019	0.244
	Placebo N=74	21	1 (4.76)	20 (95.24)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.8: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	48	32 (66.67)	16 (33.33)	4.16 (2.76, 7.36)	2.04	(1.16, 3.57)	0.018
	Placebo N=74	53	21 (39.62)	32 (60.38)	NC (6.44, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.9: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	11	5 (45.45)	6 (54.55)	NC (2.76, NC)	7.76	(0.52, 115.9)	0.717	0.635
	Placebo N=74	13	4 (30.77)	9 (69.23)	NC (1.84, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.9: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	3 (50.00)	NC (0.92, NC)	6.47	(0.57, 72.94)	0.166
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (0.92, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.9: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	30	16 (53.33)	14 (46.67)	8.28 (3.68, NC)	1.82	(0.82, 4.01)	0.140
	Placebo N=74	30	10 (33.33)	20 (66.67)	NC (6.44, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.9: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	21	14 (66.67)	7 (33.33)	3.71 (1.87, NC)	2.78	(1.10, 7.04)	0.013
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (6.44, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.1: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	30	15 (50.00)	15 (50.00)	7.36 (2.76, NC)	2.38	(1.07, 5.29)	0.037	0.578
	Placebo N=74	42	11 (26.19)	31 (73.81)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.1: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	23 (60.53)	15 (39.47)	6.44 (3.68, NC)	1.92	(0.92, 3.98)	0.056
	Placebo N=74	32	11 (34.38)	21 (65.63)	NC (6.44, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.2: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	31	19 (61.29)	12 (38.71)	6.44 (2.79, NC)	3.09	(1.46, 6.56)	0.003	0.369
	Placebo N=74	42	11 (26.19)	31 (73.81)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.2: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	37	19 (51.35)	18 (48.65)	8.28 (3.68, NC)	1.80	(0.82, 3.91)	0.233
	Placebo N=74	32	11 (34.38)	21 (65.63)	NC (4.60, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.11.1.3: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	10 (50.00)	NC (2.76, NC)	6.05	(1.48, 24.78)	0.193	0.486
	Placebo N=74	23	6 (26.09)	17 (73.91)	NC (7.36, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.11.1.3: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	22 (57.89)	16 (42.11)	6.44 (3.68, NC)	2.36	(1.18, 4.70)	0.012
	Placebo N=74	43	13 (30.23)	30 (69.77)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.11.1.3: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (2.76, NC)	0.56	(0.03, 10.54)	0.381
	Placebo N=74	5	3 (60.00)	2 (40.00)	7.39 (1.84, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.11.1.4: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	6.44 (0.92, NC)	1.08	(0.21, 5.60)	0.858	0.302
	Placebo N=74	9	6 (66.67)	3 (33.33)	4.60 (0.92, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.11.1.4: Pains-pNF, Chronic Pain - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	60	34 (56.67)	26 (43.33)	7.36 (3.68, NC)	3.09	(1.65, 5.80)	<0.001
	Placebo N=74	63	14 (22.22)	49 (77.78)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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1.1.3.1.2 Schmerz anhand PAINS-pNF – Zeit bis zur erstmaligen Verschlechterung des chronischen Schmerzes um ≥ 1,5 Punkte – Hauptanalyse

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Table 14.14.1.4: Pains-pNF, Chronic Pain - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	NC	1.000
	Placebo N=74	9	0 (0.00)	9 (100)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.14.1.4: Pains-pNF, Chronic Pain - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	60	3 (5.00)	57 (95.00)	NC (NC, NC)	0.38	(0.10, 1.42)	0.142
	Placebo N=74	63	8 (12.70)	55 (87.30)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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1.1.3.1.3 Schmerz anhand PAINS-pNF – Zeit bis zur erstmaligen Verbesserung des chronischen Schmerzes um ≥ 2 Punkte – Sensitivitätsanalyse

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Table 14.50.1.1: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	18 (60.00)	NC (2.79, NC)	2.69	(1.07, 6.78)	0.062	0.181
	Placebo N=74	42	8 (19.05)	34 (80.95)	NC (NC, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.1: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (6.44, NC)	1.25	(0.53, 2.92)	0.463
	Placebo N=74	32	9 (28.13)	23 (71.88)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.2: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	31	13 (41.94)	18 (58.06)	NC (3.68, NC)	2.92	(1.16, 7.38)	0.018	0.176
	Placebo N=74	42	7 (16.67)	35 (83.33)	NC (NC, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.2: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	37	13 (35.14)	24 (64.86)	NC (7.36, NC)	1.25	(0.53, 2.96)	0.767
	Placebo N=74	32	10 (31.25)	22 (68.75)	NC (7.36, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.3: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (3.68, NC)	8.92	(1.27, 62.51)	0.450	0.800
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.50.1.3: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (3.71, NC)	1.74	(0.77, 3.93)	0.171
	Placebo N=74	43	10 (23.26)	33 (76.74)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.50.1.3: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (2.76, NC)	54.3	(0.00, NC)	0.665
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (1.84, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.50.1.4: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	6.44 (0.92, NC)	1.91	(0.33, 10.99)	0.739	0.719
	Placebo N=74	9	5 (55.56)	4 (44.44)	7.36 (1.84, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.50.1.4: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	60	22 (36.67)	38 (63.33)	NC (9.13, NC)	2.62	(1.23, 5.56)	0.012
	Placebo N=74	63	10 (15.87)	53 (84.13)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.50.1.5: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	5 (55.56)	NC (0.92, NC)	NC	(NC, NC)	0.071	0.449
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.5: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	26	10 (38.46)	16 (61.54)	NC (7.36, NC)	2.11	(0.75, 5.92)	0.208
	Placebo N=74	27	6 (22.22)	21 (77.78)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.5: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (3.68, NC)	7.26	(0.98, 53.50)	0.368
	Placebo N=74	21	4 (19.05)	17 (80.95)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.5: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (2.79, NC)	0.71	(0.20, 2.47)	0.887
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (2.76, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.6: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (0.95, NC)	1.02	(0.27, 3.86)	0.546	0.208
	Placebo N=74	18	5 (27.78)	13 (72.22)	NC (1.84, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.50.1.6: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (1.84, NC)	NC	(NC, NC)	0.070
	Placebo N=74	12	0 (0.00)	12 (100)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.50.1.6: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	8 (50.00)	9.13 (2.79, NC)	52.9	(2.04, NC)	0.023
	Placebo N=74	11	1 (9.09)	10 (90.91)	NC (8.31, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.50.1.6: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	28	10 (35.71)	18 (64.29)	NC (6.44, NC)	1.22	(0.51, 2.93)	0.971
	Placebo N=74	32	11 (34.38)	21 (65.63)	NC (7.36, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.50.1.7: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	13 (46.43)	3.71 (2.76, NC)	3.42	(1.10, 10.67)	0.048	0.271
	Placebo N=74	19	4 (21.05)	15 (78.95)	NC (NC, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.7: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	23	8 (34.78)	15 (65.22)	NC (7.36, NC)	1.23	(0.44, 3.46)	0.607
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (7.36, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.7: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	17	3 (17.65)	14 (82.35)	NC (NC, NC)	0.94	(0.23, 3.90)	0.807
	Placebo N=74	30	6 (20.00)	24 (80.00)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.8: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Average Baseline Pains-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	NC	(NC, NC)	0.060	0.985
	Placebo N=74	21	0 (0.00)	21 (100)	NC (NC, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.8: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Average Baseline Pains-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	48	23 (47.92)	25 (52.08)	NC (3.68, NC)	1.70	(0.91, 3.20)	0.150
	Placebo N=74	53	17 (32.08)	36 (67.92)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.9: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	NC (3.68, NC)	38.8	(0.18, NC)	0.952	0.733
	Placebo N=74	13	3 (23.08)	10 (76.92)	NC (1.84, NC)				

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.9: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	3 (50.00)	NC (2.76, NC)	7.01	(0.55, 89.42)	0.183
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (0.92, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.9: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	30	11 (36.67)	19 (63.33)	NC (7.36, NC)	1.48	(0.60, 3.70)	0.426
	Placebo N=74	30	8 (26.67)	22 (73.33)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.50.1.9: Pains-pNF, Chronic Pain - Time to first improvement by 2 points threshold by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Average Chronic Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	21	9 (42.86)	12 (57.14)	NC (2.79, NC)	1.87	(0.61, 5.77)	0.114
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)			

PAINS-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least a score of 2 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.3.2 Schmerz anhand PAINS-pNF – Schmerzspitze

1.1.3.2.1 Schmerz anhand PAINS-pNF – Zeit bis zur erstmaligen Verbesserung der Schmerzspitze um ≥ 1,5 Punkte (Hauptanalyse) bzw. ≥ 2 Punkte (Sensitivitätsanalyse)

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Table 14.2.1.1: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	32	25 (78.13)	7 (21.88)	1.61 (0.95, 3.84)	1.85	(1.03, 3.31)	0.034	0.710
	Placebo N=74	42	24 (57.14)	18 (42.86)	5.59 (2.10, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.1: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	39	28 (71.79)	11 (28.21)	2.79 (0.99, 3.75)	1.55	(0.85, 2.84)	0.183
	Placebo N=74	32	18 (56.25)	14 (43.75)	4.01 (1.87, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.2: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	33	27 (81.82)	6 (18.18)	2.10 (0.43, 3.71)	2.44	(1.35, 4.40)	0.007	0.103
	Placebo N=74	42	22 (52.38)	20 (47.62)	5.59 (2.79, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.2: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	26 (68.42)	12 (31.58)	1.91 (1.15, 3.84)	1.10	(0.60, 2.00)	0.598
	Placebo N=74	32	20 (62.50)	12 (37.50)	2.79 (0.95, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.3: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	22	16 (72.73)	6 (27.27)	4.60 (0.95, 11.07)	1.54	(0.70, 3.39)	0.438	0.916
	Placebo N=74	23	13 (56.52)	10 (43.48)	5.59 (2.10, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.2.1.3: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	26 (68.42)	12 (31.58)	2.37 (1.35, 3.75)	1.56	(0.89, 2.76)	0.135
	Placebo N=74	43	23 (53.49)	20 (46.51)	6.47 (2.79, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.2.1.3: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	5 (100)	0 (0.00)	0.43 (0.03, NC)	1.02	(0.12, 8.42)	0.547
	Placebo N=74	5	5 (100)	0 (0.00)	0.95 (0.10, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.2.1.4: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	5 (100)	0 (0.00)	1.35 (0.03, NC)	2.31	(0.60, 8.90)	0.149	0.986
	Placebo N=74	9	8 (88.89)	1 (11.11)	1.97 (0.07, 4.01)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.2.1.4: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	63	45 (71.43)	18 (28.57)	2.79 (1.02, 3.75)	1.72	(1.09, 2.71)	0.014
	Placebo N=74	63	32 (50.79)	31 (49.21)	9.23 (2.79, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.2.1.5: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	9	6 (66.67)	3 (33.33)	2.37 (0.03, NC)	2.75	(0.53, 14.33)	0.179	0.911
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (1.08, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.5: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	27	19 (70.37)	8 (29.63)	2.83 (0.99, 3.84)	1.49	(0.75, 2.94)	0.198
	Placebo N=74	27	15 (55.56)	12 (44.44)	6.47 (0.95, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.5: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	18	14 (77.78)	4 (22.22)	3.71 (0.95, 10.15)	2.09	(0.88, 4.95)	0.197
	Placebo N=74	21	11 (52.38)	10 (47.62)	9.23 (0.95, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.5: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	17	14 (82.35)	3 (17.65)	1.87 (0.16, 2.40)	1.69	(0.77, 3.69)	0.235
	Placebo N=74	20	14 (70.00)	6 (30.00)	2.38 (0.26, 4.01)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.6: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	13	8 (61.54)	5 (38.46)	3.84 (0.26, NC)	0.73	(0.29, 1.82)	0.514	0.024
	Placebo N=74	18	13 (72.22)	5 (27.78)	2.27 (0.26, 6.47)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.2.1.6: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	12	10 (83.33)	2 (16.67)	1.28 (0.10, 3.71)	3.18	(0.91, 11.07)	0.015
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (0.36, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.2.1.6: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	16	13 (81.25)	3 (18.75)	2.60 (0.95, 11.07)	6.44	(1.27, 32.65)	0.016
	Placebo N=74	11	2 (18.18)	9 (81.82)	NC (0.43, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.2.1.6: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	30	22 (73.33)	8 (26.67)	2.10 (0.43, 3.75)	1.29	(0.71, 2.35)	0.354
	Placebo N=74	32	23 (71.88)	9 (28.13)	2.79 (1.87, 6.14)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 14.2.1.7: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	29	25 (86.21)	4 (13.79)	2.10 (0.36, 2.83)	2.17	(1.03, 4.58)	0.064	0.575
	Placebo N=74	19	11 (57.89)	8 (42.11)	2.79 (0.95, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.7: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	24	16 (66.67)	8 (33.33)	2.79 (0.95, 6.24)	1.30	(0.65, 2.64)	0.433
	Placebo N=74	25	16 (64.00)	9 (36.00)	3.02 (1.74, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.7: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	18	12 (66.67)	6 (33.33)	1.89 (0.95, NC)	1.28	(0.58, 2.82)	0.509
	Placebo N=74	30	15 (50.00)	15 (50.00)	9.23 (2.69, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.8: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	21	13 (61.90)	8 (38.10)	1.91 (0.95, NC)	1.44	(0.61, 3.39)	0.368	0.962
	Placebo N=74	21	10 (47.62)	11 (52.38)	NC (0.43, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.8: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	50	40 (80.00)	10 (20.00)	2.37 (0.95, 3.71)	1.72	(1.06, 2.77)	0.029
	Placebo N=74	53	32 (60.38)	21 (39.62)	3.02 (2.10, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.9: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	11	10 (90.91)	1 (9.09)	3.71 (0.95, 8.31)	1.78	(0.64, 4.94)	0.479	0.949
	Placebo N=74	13	8 (61.54)	5 (38.46)	2.79 (0.20, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.9: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	7	4 (57.14)	3 (42.86)	6.93 (0.95, NC)	2.66	(0.52, 13.62)	0.368
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (0.16, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.9: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	31	22 (70.97)	9 (29.03)	2.83 (1.02, 3.84)	1.48	(0.78, 2.79)	0.212
	Placebo N=74	30	17 (56.67)	13 (43.33)	6.14 (1.74, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.2.1.9: Pains-pNF, Spike Pain - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	22	17 (77.27)	5 (22.73)	1.45 (0.16, 2.40)	1.75	(0.85, 3.61)	0.101
	Placebo N=74	23	14 (60.87)	9 (39.13)	2.79 (1.08, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.3.2.2 Schmerz anhand PAINS-pNF – Zeit bis zur erstmaligen Verschlechterung der Schmerzspitze um ≥ 1,5 Punkte (Hauptanalyse) bzw. ≥ 2 Punkte (Sensitivitätsanalyse)

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Table 14.5.1.1: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	32	2 (6.25)	30 (93.75)	NC (NC, NC)	0.39	(0.08, 1.93)	0.147	0.502
	Placebo N=74	42	8 (19.05)	34 (80.95)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.5.1.1: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	39	3 (7.69)	36 (92.31)	NC (NC, NC)	1.01	(0.20, 5.10)	0.809
	Placebo N=74	32	3 (9.38)	29 (90.63)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.5.1.3: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	22	1 (4.55)	21 (95.45)	NC (NC, NC)	0.30	(0.03, 2.75)	0.121	0.498
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.5.1.3: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	38	4 (10.53)	34 (89.47)	NC (NC, NC)	0.84	(0.24, 3.02)	0.684
	Placebo N=74	43	6 (13.95)	37 (86.05)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.5.1.3: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	NC
	Placebo N=74	5	0 (0.00)	5 (100)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 14.5.1.4: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (0.46, NC)	1.56	(0.07, 33.23)	0.614	0.453
	Placebo N=74	9	1 (11.11)	8 (88.89)	NC (1.84, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.5.1.4: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	63	4 (6.35)	59 (93.65)	NC (NC, NC)	0.42	(0.13, 1.33)	0.109
	Placebo N=74	63	10 (15.87)	53 (84.13)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 14.5.1.8: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	21	3 (14.29)	18 (85.71)	NC (NC, NC)	1.70	(0.30, 9.68)	0.773	0.075
	Placebo N=74	21	3 (14.29)	18 (85.71)	NC (NC, NC)				

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 14.5.1.8: Pains-pNF, Spike Pain - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Maximum Spike Pain Intensity Score	Selumetinib 25 mg/m2 BID N=71	50	2 (4.00)	48 (96.00)	NC (NC, NC)	0.21	(0.04, 1.02)	0.051
	Placebo N=74	53	8 (15.09)	45 (84.91)	NC (NC, NC)			

Pains-pNF = PAin INtensity Scale for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 1.5 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.4 Endpunkt Schmerzlinderung chronischer Schmerzen

1.1.4.1 Schmerzlinderung chronischer Schmerzen – Zeit bis zur erstmaligen Schmerzlinderung – Hauptanalyse

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Table 11.1.1.6: Time to first chronic target PN pain palliation by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (0.95, NC)	0.98	(0.26, 3.75)	0.603	0.162
	Placebo N=74	17	5 (29.41)	12 (70.59)	NC (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.1.1.6: Time to first chronic target PN pain palliation by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (1.84, NC)	NC	(NC, NC)	0.070
	Placebo N=74	12	0 (0.00)	12 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.1.1.6: Time to first chronic target PN pain palliation by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	8 (50.00)	9.20 (2.79, NC)	536	(2.15, NC)	0.022
	Placebo N=74	11	1 (9.09)	10 (90.91)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.1.1.6: Time to first chronic target PN pain palliation by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	28	10 (35.71)	18 (64.29)	NC (6.44, NC)	1.19	(0.48, 2.94)	0.895
	Placebo N=74	30	11 (36.67)	19 (63.33)	NC (6.44, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.1.1.7: Time to first chronic target PN pain palliation by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	13 (46.43)	3.71 (2.76, NC)	4.45	(1.35, 14.72)	0.041	0.158
	Placebo N=74	19	4 (21.05)	15 (78.95)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.7: Time to first chronic target PN pain palliation by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	23	8 (34.78)	15 (65.22)	NC (7.36, NC)	0.98	(0.34, 2.83)	0.743
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.7: Time to first chronic target PN pain palliation by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	17	3 (17.65)	14 (82.35)	NC (NC, NC)	0.78	(0.18, 3.37)	0.780
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.8: Time to first chronic target PN pain palliation by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	NC	(NC, NC)	0.060	0.985
	Placebo N=74	21	0 (0.00)	21 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.8: Time to first chronic target PN pain palliation by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	48	23 (47.92)	25 (52.08)	NC (3.68, NC)	1.56	(0.81, 2.98)	0.202
	Placebo N=74	50	17 (34.00)	33 (66.00)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.9: Time to first chronic target PN pain palliation by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	NC (3.68, NC)	38.2	(0.18, NC)	0.938	0.684
	Placebo N=74	13	3 (23.08)	10 (76.92)	NC (7.36, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.9: Time to first chronic target PN pain palliation by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	3 (50.00)	NC (2.76, NC)	6.42	(0.53, 78.19)	0.183
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (0.92, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.9: Time to first chronic target PN pain palliation by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	30	11 (36.67)	19 (63.33)	NC (7.36, NC)	1.39	(0.56, 3.45)	0.502
	Placebo N=74	28	8 (28.57)	20 (71.43)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.9: Time to first chronic target PN pain palliation by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	21	9 (42.86)	12 (57.14)	NC (2.79, NC)	2.07	(0.60, 7.21)	0.134
	Placebo N=74	22	5 (22.73)	17 (77.27)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.1: Time to first chronic target PN pain palliation by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	18 (60.00)	NC (2.79, NC)	2.45	(0.96, 6.29)	0.080	0.249
	Placebo N=74	40	8 (20.00)	32 (80.00)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.1: Time to first chronic target PN pain palliation by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (6.44, NC)	1.36	(0.56, 3.30)	0.473
	Placebo N=74	31	9 (29.03)	22 (70.97)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.2: Time to first chronic target PN pain palliation by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	31	13 (41.94)	18 (58.06)	NC (3.68, NC)	8.36	(2.19, 31.94)	0.026	0.180
	Placebo N=74	39	7 (17.95)	32 (82.05)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.2: Time to first chronic target PN pain palliation by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	37	13 (35.14)	24 (64.86)	NC (7.36, NC)	1.32	(0.55, 3.16)	0.760
	Placebo N=74	32	10 (31.25)	22 (68.75)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.3: Time to first chronic target PN pain palliation by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (3.68, NC)	9.61	(1.35, 68.25)	0.446	0.761
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.1.1.3: Time to first chronic target PN pain palliation by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (3.71, NC)	1.81	(0.79, 4.17)	0.198
	Placebo N=74	41	10 (24.39)	31 (75.61)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.1.1.3: Time to first chronic target PN pain palliation by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (2.76, NC)	NC	(0.00, NC)	0.665
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (1.84, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.1.1.4: Time to first chronic target PN pain palliation by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	6.44 (0.92, NC)	2.91	(0.38, 22.60)	0.739	0.895
	Placebo N=74	9	5 (55.56)	4 (44.44)	7.36 (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 11.1.1.4: Time to first chronic target PN pain palliation by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	60	22 (36.67)	38 (63.33)	NC (9.20, NC)	2.54	(1.18, 5.48)	0.017
	Placebo N=74	60	10 (16.67)	50 (83.33)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 11.1.1.5: Time to first chronic target PN pain palliation by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	5 (55.56)	NC (0.92, NC)	NC	(NC, NC)	0.099	0.540
	Placebo N=74	5	0 (0.00)	5 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.5: Time to first chronic target PN pain palliation by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	26	10 (38.46)	16 (61.54)	NC (7.36, NC)	1.97	(0.71, 5.49)	0.253
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.5: Time to first chronic target PN pain palliation by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (3.68, NC)	8.17	(1.10, 60.45)	0.364
	Placebo N=74	21	4 (19.05)	17 (80.95)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.1.1.5: Time to first chronic target PN pain palliation by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (2.79, NC)	0.89	(0.22, 3.52)	0.880
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (2.76, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.4.2 Schmerzlinderung chronischer Schmerzen – Zeit bis zur erstmaligen Schmerzlinderung – Sensitivitätsanalyse I

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Table 11.4.1.1: Time to first chronic target PN pain palliation using sensitivity definition 1 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	18 (60.00)	NC (3.68, NC)	2.44	(0.95, 6.25)	0.084	0.336
	Placebo N=74	40	8 (20.00)	32 (80.00)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.1: Time to first chronic target PN pain palliation using sensitivity definition 1 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (6.44, NC)	1.41	(0.56, 3.54)	0.333
	Placebo N=74	31	8 (25.81)	23 (74.19)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.2: Time to first chronic target PN pain palliation using sensitivity definition 1 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	31	13 (41.94)	18 (58.06)	NC (3.68, NC)	7.88	(2.01, 30.81)	0.014	0.165
	Placebo N=74	39	6 (15.38)	33 (84.62)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.2: Time to first chronic target PN pain palliation using sensitivity definition 1 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	37	13 (35.14)	24 (64.86)	NC (7.36, NC)	1.34	(0.56, 3.20)	0.772
	Placebo N=74	32	10 (31.25)	22 (68.75)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.3: Time to first chronic target PN pain palliation using sensitivity definition 1 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (3.68, NC)	9.61	(1.35, 68.25)	0.446	0.784
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.4.1.3: Time to first chronic target PN pain palliation using sensitivity definition 1 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (6.44, NC)	1.91	(0.81, 4.53)	0.137
	Placebo N=74	41	9 (21.95)	32 (78.05)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.4.1.3: Time to first chronic target PN pain palliation using sensitivity definition 1 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (2.76, NC)	NC	(0.00, NC)	0.665
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (1.84, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.4.1.4: Time to first chronic target PN pain palliation using sensitivity definition 1 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	6.44 (0.92, NC)	2.91	(0.38, 22.60)	0.739	0.754
	Placebo N=74	9	5 (55.56)	4 (44.44)	7.36 (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 11.4.1.4: Time to first chronic target PN pain palliation using sensitivity definition 1 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	60	22 (36.67)	38 (63.33)	NC (8.28, NC)	2.74	(1.24, 6.08)	0.010
	Placebo N=74	60	9 (15.00)	51 (85.00)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 11.4.1.5: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	5 (55.56)	NC (0.92, NC)	NC	(NC, NC)	0.099	0.430
	Placebo N=74	5	0 (0.00)	5 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.5: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	26	10 (38.46)	16 (61.54)	NC (7.36, NC)	2.37	(0.80, 6.97)	0.153
	Placebo N=74	25	5 (20.00)	20 (80.00)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.5: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (3.68, NC)	8.17	(1.10, 60.45)	0.364
	Placebo N=74	21	4 (19.05)	17 (80.95)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.5: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (2.79, NC)	0.89	(0.22, 3.52)	0.880
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (2.76, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.6: Time to first chronic target PN pain palliation using sensitivity definition 1 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (0.95, NC)	0.96	(0.25, 3.70)	0.613	0.183
	Placebo N=74	17	5 (29.41)	12 (70.59)	NC (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.4.1.6: Time to first chronic target PN pain palliation using sensitivity definition 1 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (1.84, NC)	NC	(NC, NC)	0.070
	Placebo N=74	12	0 (0.00)	12 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.4.1.6: Time to first chronic target PN pain palliation using sensitivity definition 1 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	8 (50.00)	9.20 (3.68, NC)	148	(1.52, NC)	0.022
	Placebo N=74	11	1 (9.09)	10 (90.91)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.4.1.6: Time to first chronic target PN pain palliation using sensitivity definition 1 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	28	10 (35.71)	18 (64.29)	NC (6.44, NC)	1.26	(0.50, 3.18)	0.916
	Placebo N=74	30	10 (33.33)	20 (66.67)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.4.1.7: Time to first chronic target PN pain palliation using sensitivity definition 1 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	13 (46.43)	6.44 (2.76, NC)	5.46	(1.45, 20.56)	0.021	0.100
	Placebo N=74	19	3 (15.79)	16 (84.21)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.7: Time to first chronic target PN pain palliation using sensitivity definition 1 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	23	8 (34.78)	15 (65.22)	NC (7.36, NC)	0.97	(0.34, 2.79)	0.751
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.7: Time to first chronic target PN pain palliation using sensitivity definition 1 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	17	3 (17.65)	14 (82.35)	NC (NC, NC)	0.78	(0.18, 3.37)	0.780
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.8: Time to first chronic target PN pain palliation using sensitivity definition 1 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	NC	(NC, NC)	0.060	0.986
	Placebo N=74	21	0 (0.00)	21 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.8: Time to first chronic target PN pain palliation using sensitivity definition 1 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	48	23 (47.92)	25 (52.08)	NC (3.71, NC)	1.60	(0.83, 3.11)	0.157
	Placebo N=74	50	16 (32.00)	34 (68.00)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.9: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	NC (3.68, NC)	38.2	(0.18, NC)	0.938	0.733
	Placebo N=74	13	3 (23.08)	10 (76.92)	NC (7.36, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.9: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	3 (50.00)	NC (2.76, NC)	6.42	(0.53, 78.19)	0.183
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (0.92, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.9: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	30	11 (36.67)	19 (63.33)	NC (7.36, NC)	1.59	(0.61, 4.10)	0.350
	Placebo N=74	28	7 (25.00)	21 (75.00)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.4.1.9: Time to first chronic target PN pain palliation using sensitivity definition 1 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 1)	Selumetinib 25 mg/m2 BID N=71	21	9 (42.86)	12 (57.14)	NC (2.79, NC)	2.07	(0.60, 7.21)	0.134
	Placebo N=74	22	5 (22.73)	17 (77.27)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 1 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and chronic pain medication score.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.4.3 Schmerzlinderung chronischer Schmerzen – Zeit bis zur erstmaligen Schmerzlinderung – Sensitivitätsanalyse II

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Table 11.7.1.6: Time to first chronic target PN pain palliation using sensitivity definition 2 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (0.95, NC)	0.96	(0.25, 3.70)	0.613	0.162
	Placebo N=74	17	5 (29.41)	12 (70.59)	NC (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.7.1.6: Time to first chronic target PN pain palliation using sensitivity definition 2 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (1.84, NC)	NC	(NC, NC)	0.070
	Placebo N=74	12	0 (0.00)	12 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.7.1.6: Time to first chronic target PN pain palliation using sensitivity definition 2 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	8 (50.00)	9.20 (2.79, NC)	507	(2.12, NC)	0.023
	Placebo N=74	11	1 (9.09)	10 (90.91)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.7.1.6: Time to first chronic target PN pain palliation using sensitivity definition 2 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	28	10 (35.71)	18 (64.29)	NC (6.44, NC)	1.24	(0.51, 3.00)	0.950
	Placebo N=74	31	11 (35.48)	20 (64.52)	NC (6.44, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 11.7.1.7: Time to first chronic target PN pain palliation using sensitivity definition 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	13 (46.43)	3.71 (2.76, NC)	4.19	(1.28, 13.71)	0.049	0.208
	Placebo N=74	19	4 (21.05)	15 (78.95)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.7: Time to first chronic target PN pain palliation using sensitivity definition 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	23	8 (34.78)	15 (65.22)	NC (7.36, NC)	1.06	(0.37, 3.04)	0.675
	Placebo N=74	24	7 (29.17)	17 (70.83)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.7: Time to first chronic target PN pain palliation using sensitivity definition 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	17	3 (17.65)	14 (82.35)	NC (NC, NC)	0.78	(0.18, 3.37)	0.780
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.8: Time to first chronic target PN pain palliation using sensitivity definition 2 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	NC	(NC, NC)	0.060	0.985
	Placebo N=74	21	0 (0.00)	21 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.8: Time to first chronic target PN pain palliation using sensitivity definition 2 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	48	23 (47.92)	25 (52.08)	NC (3.68, NC)	1.63	(0.86, 3.10)	0.184
	Placebo N=74	51	17 (33.33)	34 (66.67)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.9: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	NC (3.68, NC)	355	(0.17, NC)	0.965	0.649
	Placebo N=74	13	3 (23.08)	10 (76.92)	NC (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.9: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	3 (50.00)	NC (2.76, NC)	6.42	(0.53, 78.19)	0.183
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (0.92, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.9: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	30	11 (36.67)	19 (63.33)	NC (7.36, NC)	1.38	(0.56, 3.44)	0.505
	Placebo N=74	28	8 (28.57)	20 (71.43)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.9: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	21	9 (42.86)	12 (57.14)	NC (2.79, NC)	2.32	(0.70, 7.74)	0.114
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.1: Time to first chronic target PN pain palliation using sensitivity definition 2 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	18 (60.00)	NC (2.79, NC)	2.58	(1.01, 6.59)	0.073	0.229
	Placebo N=74	41	8 (19.51)	33 (80.49)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.1: Time to first chronic target PN pain palliation using sensitivity definition 2 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (6.44, NC)	1.34	(0.55, 3.26)	0.481
	Placebo N=74	31	9 (29.03)	22 (70.97)	NC (8.31, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.2: Time to first chronic target PN pain palliation using sensitivity definition 2 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	31	13 (41.94)	18 (58.06)	NC (3.68, NC)	8.57	(2.28, 32.29)	0.023	0.156
	Placebo N=74	40	7 (17.50)	33 (82.50)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.2: Time to first chronic target PN pain palliation using sensitivity definition 2 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	37	13 (35.14)	24 (64.86)	NC (7.36, NC)	1.32	(0.55, 3.16)	0.759
	Placebo N=74	32	10 (31.25)	22 (68.75)	NC (7.36, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.3: Time to first chronic target PN pain palliation using sensitivity definition 2 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (3.68, NC)	9.51	(1.34, 67.76)	0.458	0.777
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.7.1.3: Time to first chronic target PN pain palliation using sensitivity definition 2 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (3.71, NC)	1.79	(0.78, 4.13)	0.202
	Placebo N=74	41	10 (24.39)	31 (75.61)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.7.1.3: Time to first chronic target PN pain palliation using sensitivity definition 2 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (2.76, NC)	NC	(0.00, NC)	0.665
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (1.84, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 11.7.1.4: Time to first chronic target PN pain palliation using sensitivity definition 2 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	6.44 (0.92, NC)	2.91	(0.38, 22.60)	0.739	0.910
	Placebo N=74	9	5 (55.56)	4 (44.44)	7.36 (1.84, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 11.7.1.4: Time to first chronic target PN pain palliation using sensitivity definition 2 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	60	22 (36.67)	38 (63.33)	NC (7.36, NC)	2.57	(1.20, 5.51)	0.015
	Placebo N=74	61	10 (16.39)	51 (83.61)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 11.7.1.5: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	5 (55.56)	NC (0.92, NC)	NC	(NC, NC)	0.071	0.554
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.5: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	26	10 (38.46)	16 (61.54)	NC (7.36, NC)	1.96	(0.70, 5.46)	0.255
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.5: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (3.68, NC)	8.08	(1.09, 60.05)	0.373
	Placebo N=74	21	4 (19.05)	17 (80.95)	NC (NC, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 11.7.1.5: Time to first chronic target PN pain palliation using sensitivity definition 2 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (months), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Palliation (Sensitivity 2)	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (2.79, NC)	0.88	(0.22, 3.49)	0.887
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (2.76, NC)			

CI = Confidence interval
Time to first chronic target PN pain palliation is time from randomisation to last day of the first cycle where pain palliation as per sensitivity definition 2 is achieved.
Subjects with no pain palliation are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score and baseline pain medication score as covariates.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available for chronic pain intensity score and investigator pain medication assessment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5 Endpunkt Schmerz anhand PGIC

1.1.5.1 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – chronischer Schmerz

1.1.5.1.1 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verbesserung des chronischen Schmerzes – Hauptanalyse

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Table 17.2.1.8: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	14 (70.00)	6 (30.00)	51.00 (29.00, 281.00)	2.13	(0.92, 4.97)	0.058	0.476
	Placebo N=74	21	10 (47.62)	11 (52.38)	NC (58.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.8: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	40 (83.33)	8 (16.67)	35.00 (29.00, 63.00)	1.52	(0.95, 2.41)	0.071
	Placebo N=74	53	37 (69.81)	16 (30.19)	58.00 (56.00, 165.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	10 (90.91)	1 (9.09)	112.00 (27.00, 175.00)	1.31	(0.47, 3.61)	0.750	0.149
	Placebo N=74	13	11 (84.62)	2 (15.38)	56.00 (27.00, 114.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	5 (83.33)	1 (16.67)	84.50 (29.00, NC)	13.3	(1.47, 120.5)	0.015
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (168.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	21 (70.00)	9 (30.00)	55.00 (29.00, 171.00)	1.25	(0.67, 2.31)	0.441
	Placebo N=74	30	20 (66.67)	10 (33.33)	84.00 (57.00, 177.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	18 (85.71)	3 (14.29)	30.00 (28.00, 58.00)	2.29	(1.11, 4.70)	0.012
	Placebo N=74	23	14 (60.87)	9 (39.13)	112.00 (31.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.1: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	24 (80.00)	6 (20.00)	57.00 (29.00, 114.00)	1.24	(0.69, 2.22)	0.192	0.526
	Placebo N=74	42	28 (66.67)	14 (33.33)	60.00 (57.00, 224.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.1: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	30 (78.95)	8 (21.05)	42.50 (29.00, 58.00)	1.73	(0.95, 3.14)	0.027
	Placebo N=74	32	19 (59.38)	13 (40.63)	165.00 (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.2: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	26 (83.87)	5 (16.13)	34.00 (29.00, 113.00)	1.92	(1.10, 3.36)	0.014	0.334
	Placebo N=74	42	25 (59.52)	17 (40.48)	165.00 (57.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.2: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	28 (75.68)	9 (24.32)	55.00 (30.00, 113.00)	1.14	(0.63, 2.06)	0.403
	Placebo N=74	32	22 (68.75)	10 (31.25)	58.00 (29.00, 114.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.3: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	18 (90.00)	2 (10.00)	55.00 (29.00, 114.00)	1.97	(0.92, 4.23)	0.093	0.373
	Placebo N=74	23	15 (65.22)	8 (34.78)	114.00 (56.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.2.1.3: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	28 (73.68)	10 (26.32)	55.00 (29.00, 113.00)	1.57	(0.92, 2.69)	0.091
	Placebo N=74	43	26 (60.47)	17 (39.53)	109.00 (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.2.1.3: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	2 (50.00)	NC (35.00, NC)	NC	(0.01, NC)	0.305
	Placebo N=74	5	4 (80.00)	1 (20.00)	64.00 (28.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.2.1.4: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	1 (20.00)	29.00 (28.00, NC)	0.91	(0.21, 3.90)	0.895	0.250
	Placebo N=74	9	9 (100)	0 (0.00)	29.00 (28.00, 64.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.2.1.4: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	48 (80.00)	12 (20.00)	53.00 (29.00, 112.00)	1.96	(1.26, 3.04)	0.002
	Placebo N=74	63	36 (57.14)	27 (42.86)	168.00 (58.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.2.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	9 (100)	0 (0.00)	29.00 (25.00, 63.00)	18.3	(2.09, 160.3)	0.001	0.045
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (58.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	18 (69.23)	8 (30.77)	55.00 (29.00, 288.00)	1.52	(0.77, 3.01)	0.220
	Placebo N=74	27	17 (62.96)	10 (37.04)	109.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	15 (88.24)	2 (11.76)	112.00 (29.00, 175.00)	2.08	(0.88, 4.94)	0.156
	Placebo N=74	21	13 (61.90)	8 (38.10)	168.00 (54.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	12 (75.00)	4 (25.00)	30.00 (29.00, 169.00)	0.81	(0.34, 1.91)	0.931
	Placebo N=74	20	15 (75.00)	5 (25.00)	43.50 (29.00, 112.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	9 (75.00)	3 (25.00)	51.00 (28.00, 169.00)	1.47	(0.58, 3.70)	0.413	0.734
	Placebo N=74	18	12 (66.67)	6 (33.33)	57.00 (29.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.2.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	7 (58.33)	5 (41.67)	224.50 (28.00, NC)	1.39	(0.39, 4.90)	0.600
	Placebo N=74	12	6 (50.00)	6 (50.00)	NC (30.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.2.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	13 (81.25)	3 (18.75)	55.00 (29.00, 114.00)	2.30	(0.72, 7.38)	0.096
	Placebo N=74	11	6 (54.55)	5 (45.45)	168.00 (54.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.2.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	25 (89.29)	3 (10.71)	30.00 (29.00, 112.00)	1.95	(1.07, 3.56)	0.076
	Placebo N=74	32	23 (71.88)	9 (28.13)	58.00 (56.00, 114.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.2.1.7: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	25 (89.29)	3 (10.71)	33.00 (29.00, 58.00)	2.33	(1.13, 4.80)	0.027	0.329
	Placebo N=74	19	12 (63.16)	7 (36.84)	114.00 (29.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.7: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	23	18 (78.26)	5 (21.74)	55.00 (28.00, 114.00)	1.78	(0.88, 3.59)	0.144
	Placebo N=74	25	16 (64.00)	9 (36.00)	106.00 (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.2.1.7: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	11 (64.71)	6 (35.29)	57.00 (29.00, NC)	1.12	(0.53, 2.38)	0.873
	Placebo N=74	30	19 (63.33)	11 (36.67)	87.50 (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.1.2 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verschlechterung des chronischen Schmerzes – Hauptanalyse

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Table 17.5.1.1: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	6 (20.00)	24 (80.00)	NC (NC, NC)	0.82	(0.30, 2.25)	0.397	0.366
	Placebo N=74	42	12 (28.57)	30 (71.43)	351.00 (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.1: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	7 (18.42)	31 (81.58)	NC (NC, NC)	0.42	(0.17, 1.08)	0.052
	Placebo N=74	32	14 (43.75)	18 (56.25)	351.00 (169.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.2: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	9 (29.03)	22 (70.97)	NC (NC, NC)	0.73	(0.31, 1.70)	0.313	0.395
	Placebo N=74	42	18 (42.86)	24 (57.14)	351.00 (223.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.2: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	4 (10.81)	33 (89.19)	NC (NC, NC)	0.41	(0.12, 1.37)	0.193
	Placebo N=74	32	8 (25.00)	24 (75.00)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.3: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	0.39	(0.09, 1.70)	0.337	0.990
	Placebo N=74	23	6 (26.09)	17 (73.91)	NC (336.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.5.1.3: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	7 (18.42)	31 (81.58)	NC (NC, NC)	0.48	(0.20, 1.17)	0.090
	Placebo N=74	43	18 (41.86)	25 (58.14)	351.00 (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.5.1.3: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (282.00, NC)	NC	(0.00, NC)	0.665
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.5.1.4: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (172.00, NC)	0.00	(0.00, NC)	0.209	0.554
	Placebo N=74	9	5 (55.56)	4 (44.44)	330.00 (28.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.5.1.4: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	11 (18.33)	49 (81.67)	NC (NC, NC)	0.55	(0.26, 1.17)	0.144
	Placebo N=74	63	21 (33.33)	42 (66.67)	351.00 (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.5.1.5: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	2 (22.22)	7 (77.78)	NC (57.00, NC)	0.80	(0.11, 5.83)	0.853	0.638
	Placebo N=74	6	3 (50.00)	3 (50.00)	351.00 (176.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.5: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	5 (19.23)	21 (80.77)	NC (NC, NC)	0.42	(0.14, 1.22)	0.062
	Placebo N=74	27	12 (44.44)	15 (55.56)	351.00 (60.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.5: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	1 (5.88)	16 (94.12)	NC (NC, NC)	0.19	(0.02, 1.66)	0.110
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (336.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.5: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	5 (31.25)	11 (68.75)	NC (169.00, NC)	0.86	(0.26, 2.91)	0.892
	Placebo N=74	20	6 (30.00)	14 (70.00)	NC (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.6: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	4 (33.33)	8 (66.67)	NC (54.00, NC)	1.37	(0.33, 5.75)	0.515	0.498
	Placebo N=74	18	4 (22.22)	14 (77.78)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.5.1.6: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	0 (0.00)	12 (100)	NC (NC, NC)	NC	(NC, NC)	0.078
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (176.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.5.1.6: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	4 (25.00)	12 (75.00)	NC (169.00, NC)	0.28	(0.04, 1.84)	0.326
	Placebo N=74	11	5 (45.45)	6 (54.55)	336.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.5.1.6: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	5 (17.86)	23 (82.14)	NC (NC, NC)	0.36	(0.13, 1.02)	0.049
	Placebo N=74	32	14 (43.75)	18 (56.25)	351.00 (223.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.5.1.7: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	6 (21.43)	22 (78.57)	NC (NC, NC)	0.28	(0.10, 0.79)	0.011	0.113
	Placebo N=74	19	11 (57.89)	8 (42.11)	226.00 (105.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.7: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	23	6 (26.09)	17 (73.91)	NC (225.00, NC)	1.24	(0.39, 3.93)	0.742
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.7: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	1 (5.88)	16 (94.12)	NC (NC, NC)	0.18	(0.02, 1.43)	0.064
	Placebo N=74	30	9 (30.00)	21 (70.00)	NC (336.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.8: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	2 (10.00)	18 (90.00)	NC (NC, NC)	0.11	(0.01, 1.42)	0.798	0.712
	Placebo N=74	21	3 (14.29)	18 (85.71)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.8: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	11 (22.92)	37 (77.08)	NC (NC, NC)	0.49	(0.24, 1.00)	0.038
	Placebo N=74	53	23 (43.40)	30 (56.60)	351.00 (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.9: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	0 (0.00)	11 (100)	NC (NC, NC)	NC	(NC, NC)	0.338	0.934
	Placebo N=74	13	1 (7.69)	12 (92.31)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.9: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (169.00, NC)	0.12	(0.01, 1.49)	0.173
	Placebo N=74	8	4 (50.00)	4 (50.00)	336.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.9: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	7 (23.33)	23 (76.67)	NC (NC, NC)	0.62	(0.24, 1.58)	0.213
	Placebo N=74	30	12 (40.00)	18 (60.00)	351.00 (169.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.5.1.9: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	5 (23.81)	16 (76.19)	NC (225.00, NC)	0.57	(0.18, 1.77)	0.488
	Placebo N=74	23	9 (39.13)	14 (60.87)	351.00 (226.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.1.3 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verbesserung des chronischen Schmerzes – Sensitivitätsanalyse

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Table 17.8.1.1: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	17 (56.67)	13 (43.33)	168.00 (53.00, NC)	1.66	(0.82, 3.35)	0.053	0.916
	Placebo N=74	42	15 (35.71)	27 (64.29)	NC (168.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.1: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	18 (47.37)	20 (52.63)	NC (115.00, NC)	1.85	(0.86, 4.00)	0.203
	Placebo N=74	32	11 (34.38)	21 (65.63)	NC (177.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.2: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	18 (58.06)	13 (41.94)	169.00 (106.00, NC)	2.87	(1.34, 6.16)	0.010	0.062
	Placebo N=74	42	11 (26.19)	31 (73.81)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.2: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	17 (45.95)	20 (54.05)	333.00 (113.00, NC)	1.03	(0.49, 2.15)	0.676
	Placebo N=74	32	15 (46.88)	17 (53.13)	NC (118.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.3: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	11 (55.00)	9 (45.00)	252.50 (58.00, NC)	5.12	(1.47, 17.86)	0.065	0.360
	Placebo N=74	23	6 (26.09)	17 (73.91)	NC (278.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.8.1.3: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	18 (47.37)	20 (52.63)	333.00 (113.00, NC)	1.48	(0.75, 2.90)	0.277
	Placebo N=74	43	16 (37.21)	27 (62.79)	NC (168.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.8.1.3: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (35.00, NC)	0.86	(0.04, 17.71)	0.449
	Placebo N=74	5	3 (60.00)	2 (40.00)	177.00 (162.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.8.1.4: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	1 (20.00)	57.00 (29.00, NC)	2.86	(0.47, 17.46)	0.806	0.477
	Placebo N=74	9	6 (66.67)	3 (33.33)	176.00 (29.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.8.1.4: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	30 (50.00)	30 (50.00)	169.00 (114.00, NC)	2.08	(1.16, 3.74)	0.012
	Placebo N=74	63	18 (28.57)	45 (71.43)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.8.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	5 (55.56)	4 (44.44)	165.00 (34.00, NC)	NC	(NC, NC)	0.035	0.788
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	12 (46.15)	14 (53.85)	NC (35.00, NC)	1.29	(0.55, 3.02)	0.384
	Placebo N=74	27	10 (37.04)	17 (62.96)	NC (162.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	9 (52.94)	8 (47.06)	336.00 (113.00, NC)	3.73	(1.05, 13.22)	0.084
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (278.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.5: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	9 (56.25)	7 (43.75)	113.00 (29.00, NC)	1.11	(0.43, 2.83)	0.677
	Placebo N=74	20	11 (55.00)	9 (45.00)	176.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (116.00, NC)	0.75	(0.23, 2.49)	0.605	0.406
	Placebo N=74	18	8 (44.44)	10 (55.56)	NC (58.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.8.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	7 (58.33)	5 (41.67)	224.50 (28.00, NC)	3.92	(0.76, 20.26)	0.115
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (106.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.8.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	7 (43.75)	9 (56.25)	NC (57.00, NC)	3.34	(0.48, 23.07)	0.104
	Placebo N=74	11	2 (18.18)	9 (81.82)	NC (162.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.8.1.6: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	16 (57.14)	12 (42.86)	165.00 (31.00, NC)	1.62	(0.77, 3.40)	0.128
	Placebo N=74	32	13 (40.63)	19 (59.38)	NC (118.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.8.1.7: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	18 (64.29)	10 (35.71)	85.50 (35.00, NC)	2.85	(1.11, 7.31)	0.029	0.100
	Placebo N=74	19	6 (31.58)	13 (68.42)	NC (109.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.7: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	23	12 (52.17)	11 (47.83)	333.00 (113.00, NC)	1.95	(0.79, 4.83)	0.134
	Placebo N=74	25	8 (32.00)	17 (68.00)	NC (278.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.7: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	5 (29.41)	12 (70.59)	NC (114.00, NC)	0.77	(0.27, 2.24)	0.547
	Placebo N=74	30	12 (40.00)	18 (60.00)	NC (113.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.8: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	9 (45.00)	11 (55.00)	NC (29.00, NC)	1.26	(0.48, 3.28)	0.512	0.655
	Placebo N=74	21	9 (42.86)	12 (57.14)	NC (112.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.8: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	26 (54.17)	22 (45.83)	169.00 (113.00, NC)	1.91	(1.03, 3.57)	0.031
	Placebo N=74	53	17 (32.08)	36 (67.92)	NC (284.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	8 (72.73)	3 (27.27)	168.00 (57.00, NC)	4.95	(1.08, 22.73)	0.063	0.492
	Placebo N=74	13	4 (30.77)	9 (69.23)	NC (112.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (169.00, NC)	1.46	(0.09, 23.56)	0.788
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (274.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	13 (43.33)	17 (56.67)	NC (35.00, NC)	1.03	(0.47, 2.23)	0.798
	Placebo N=74	30	13 (43.33)	17 (56.67)	NC (113.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.8.1.9: PGIC, Chronic pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	13 (61.90)	8 (38.10)	113.00 (51.00, NC)	2.31	(0.95, 5.64)	0.044
	Placebo N=74	23	8 (34.78)	15 (65.22)	NC (168.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in chronic pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.1.4 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verschlechterung des chronischen Schmerzes – Sensitivitätsanalyse

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Table 17.11.1.2: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	5 (16.13)	26 (83.87)	NC (NC, NC)	1.24	(0.37, 4.18)	0.993	0.294
	Placebo N=74	42	6 (14.29)	36 (85.71)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.11.1.2: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	1 (2.70)	36 (97.30)	NC (NC, NC)	0.27	(0.03, 2.61)	0.300
	Placebo N=74	32	3 (9.38)	29 (90.63)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.11.1.3: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	1 (5.00)	19 (95.00)	NC (NC, NC)	0.36	(0.02, 5.36)	0.548	0.817
	Placebo N=74	23	2 (8.70)	21 (91.30)	NC (338.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.11.1.3: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	5 (13.16)	33 (86.84)	NC (NC, NC)	1.19	(0.34, 4.11)	0.789
	Placebo N=74	43	5 (11.63)	38 (88.37)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.11.1.3: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	0 (0.00)	4 (100)	NC (NC, NC)	NC	(NC, NC)	0.180
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (280.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.11.1.4: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	0.117	0.995
	Placebo N=74	9	3 (33.33)	6 (66.67)	NC (28.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.11.1.4: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	6 (10.00)	54 (90.00)	NC (NC, NC)	1.14	(0.36, 3.59)	0.907
	Placebo N=74	63	6 (9.52)	57 (90.48)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.11.1.8: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	0 (0.00)	20 (100)	NC (NC, NC)	NC	(NC, NC)	0.187	0.994
	Placebo N=74	21	2 (9.52)	19 (90.48)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.11.1.8: PGIC, Chronic pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Chronic pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	6 (12.50)	42 (87.50)	NC (NC, NC)	0.93	(0.31, 2.79)	0.848
	Placebo N=74	53	7 (13.21)	46 (86.79)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in chronic pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.2 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Schmerzspitze

1.1.5.2.1 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verbesserung der Schmerzspitze – Hauptanalyse

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Table 17.17.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	10 (90.91)	1 (9.09)	29.00 (27.00, 112.00)	1.38	(0.54, 3.55)	0.937	0.272
	Placebo N=74	13	12 (92.31)	1 (7.69)	29.00 (27.00, 57.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	5 (83.33)	1 (16.67)	168.50 (29.00, NC)	4.00	(0.76, 21.19)	0.080
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	22 (73.33)	8 (26.67)	55.00 (29.00, 116.00)	1.70	(0.91, 3.20)	0.078
	Placebo N=74	30	18 (60.00)	12 (40.00)	162.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	20 (95.24)	1 (4.76)	30.00 (29.00, 51.00)	2.47	(1.19, 5.11)	0.002
	Placebo N=74	23	14 (60.87)	9 (39.13)	112.00 (31.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.8: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	16 (80.00)	4 (20.00)	51.00 (29.00, 113.00)	2.45	(1.08, 5.58)	0.019	0.391
	Placebo N=74	21	11 (52.38)	10 (47.62)	274.00 (57.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.8: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	41 (85.42)	7 (14.58)	31.00 (29.00, 58.00)	1.66	(1.05, 2.63)	0.018
	Placebo N=74	53	36 (67.92)	17 (32.08)	106.00 (38.00, 173.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.7: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	26 (92.86)	2 (7.14)	30.00 (29.00, 58.00)	2.81	(1.37, 5.76)	0.010	0.380
	Placebo N=74	19	12 (63.16)	7 (36.84)	166.00 (38.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.7: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	23	19 (82.61)	4 (17.39)	31.00 (29.00, 111.00)	1.53	(0.80, 2.95)	0.087
	Placebo N=74	25	18 (72.00)	7 (28.00)	58.00 (32.00, 281.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.7: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	12 (70.59)	5 (29.41)	112.00 (30.00, 281.00)	1.37	(0.65, 2.91)	0.399
	Placebo N=74	30	17 (56.67)	13 (43.33)	162.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	9 (75.00)	3 (25.00)	32.50 (28.00, NC)	2.17	(0.80, 5.86)	0.135	0.719
	Placebo N=74	18	10 (55.56)	8 (44.44)	166.00 (29.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.17.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	9 (75.00)	3 (25.00)	85.00 (28.00, NC)	3.77	(1.01, 14.08)	0.066
	Placebo N=74	12	6 (50.00)	6 (50.00)	NC (30.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.17.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	13 (81.25)	3 (18.75)	53.00 (30.00, 113.00)	4.22	(1.14, 15.55)	0.081
	Placebo N=74	11	7 (63.64)	4 (36.36)	162.00 (54.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.17.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	26 (92.86)	2 (7.14)	30.00 (29.00, 112.00)	1.42	(0.79, 2.57)	0.128
	Placebo N=74	32	24 (75.00)	8 (25.00)	57.00 (29.00, 112.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.17.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	9 (100)	0 (0.00)	34.00 (28.00, 113.00)	5.78	(1.15, 29.08)	0.010	0.359
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (38.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	20 (76.92)	6 (23.08)	55.00 (29.00, 116.00)	1.99	(1.01, 3.92)	0.031
	Placebo N=74	27	15 (55.56)	12 (44.44)	169.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	15 (88.24)	2 (11.76)	53.00 (28.00, 113.00)	1.75	(0.79, 3.89)	0.320
	Placebo N=74	21	15 (71.43)	6 (28.57)	57.00 (28.00, 274.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	13 (81.25)	3 (18.75)	30.00 (29.00, 57.00)	1.39	(0.63, 3.09)	0.239
	Placebo N=74	20	15 (75.00)	5 (25.00)	56.00 (29.00, 173.00)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.4: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	5 (100)	0 (0.00)	29.00 (28.00, NC)	1.58	(0.41, 6.13)	0.333	0.835
	Placebo N=74	9	9 (100)	0 (0.00)	29.00 (28.00, 112.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.17.1.4: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	50 (83.33)	10 (16.67)	34.00 (29.00, 111.00)	2.14	(1.38, 3.30)	<0.001
	Placebo N=74	63	36 (57.14)	27 (42.86)	168.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.17.1.3: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	18 (90.00)	2 (10.00)	43.50 (29.00, 112.00)	1.96	(0.93, 4.12)	0.145	0.628
	Placebo N=74	23	16 (69.57)	7 (30.43)	57.00 (29.00, 274.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.17.1.3: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	30 (78.95)	8 (21.05)	34.00 (29.00, 58.00)	2.03	(1.19, 3.47)	0.008
	Placebo N=74	43	25 (58.14)	18 (41.86)	113.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.17.1.3: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	3 (75.00)	1 (25.00)	229.50 (35.00, NC)	0.62	(0.06, 6.40)	0.624
	Placebo N=74	5	4 (80.00)	1 (20.00)	162.00 (28.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.17.1.2: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	28 (90.32)	3 (9.68)	31.00 (29.00, 58.00)	1.96	(1.14, 3.38)	0.005	0.754
	Placebo N=74	42	27 (64.29)	15 (35.71)	114.00 (57.00, 281.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.2: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	29 (78.38)	8 (21.62)	35.00 (30.00, 112.00)	1.58	(0.88, 2.85)	0.092
	Placebo N=74	32	20 (62.50)	12 (37.50)	57.00 (30.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.1: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	26 (86.67)	4 (13.33)	35.00 (29.00, 113.00)	1.45	(0.84, 2.50)	0.073	0.414
	Placebo N=74	42	29 (69.05)	13 (30.95)	58.00 (57.00, 169.00)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.17.1.1: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 or 3 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	31 (81.58)	7 (18.42)	31.00 (29.00, 57.00)	2.07	(1.12, 3.85)	0.005
	Placebo N=74	32	18 (56.25)	14 (43.75)	173.00 (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2 or 3.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.2.2 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verschlechterung der Schmerzspitze – Hauptanalyse

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Table 17.20.1.1: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	7 (23.33)	23 (76.67)	NC (NC, NC)	0.75	(0.30, 1.89)	0.251	0.721
	Placebo N=74	42	16 (38.10)	26 (61.90)	351.00 (281.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.1: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	9 (23.68)	29 (76.32)	NC (NC, NC)	0.59	(0.24, 1.42)	0.256
	Placebo N=74	32	12 (37.50)	20 (62.50)	NC (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.2: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	11 (35.48)	20 (64.52)	NC (225.00, NC)	0.79	(0.36, 1.70)	0.424	0.431
	Placebo N=74	42	19 (45.24)	23 (54.76)	336.00 (223.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.2: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	5 (13.51)	32 (86.49)	NC (NC, NC)	0.45	(0.15, 1.36)	0.229
	Placebo N=74	32	9 (28.13)	23 (71.88)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.3: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	4 (20.00)	16 (80.00)	NC (NC, NC)	0.51	(0.14, 1.81)	0.430	0.954
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (281.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.20.1.3: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	8 (21.05)	30 (78.95)	NC (NC, NC)	0.48	(0.21, 1.12)	0.075
	Placebo N=74	43	19 (44.19)	24 (55.81)	351.00 (176.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.20.1.3: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (29.00, NC)	NC	(0.00, NC)	0.771
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.20.1.4: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (172.00, NC)	0.00	(0.00, NC)	0.184	0.458
	Placebo N=74	9	5 (55.56)	4 (44.44)	330.00 (28.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.20.1.4: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	14 (23.33)	46 (76.67)	NC (NC, NC)	0.62	(0.31, 1.23)	0.226
	Placebo N=74	63	23 (36.51)	40 (63.49)	351.00 (336.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.20.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	3 (33.33)	6 (66.67)	NC (57.00, NC)	0.79	(0.15, 4.11)	0.881	0.634
	Placebo N=74	6	3 (50.00)	3 (50.00)	NC (170.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	5 (19.23)	21 (80.77)	NC (NC, NC)	0.44	(0.15, 1.25)	0.054
	Placebo N=74	27	13 (48.15)	14 (51.85)	351.00 (125.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	2 (11.76)	15 (88.24)	NC (NC, NC)	0.38	(0.08, 1.93)	0.187
	Placebo N=74	21	6 (28.57)	15 (71.43)	NC (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (169.00, NC)	1.02	(0.32, 3.23)	0.675
	Placebo N=74	20	6 (30.00)	14 (70.00)	NC (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.6: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	4 (33.33)	8 (66.67)	NC (29.00, NC)	1.43	(0.34, 6.13)	0.480	0.353
	Placebo N=74	18	4 (22.22)	14 (77.78)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.20.1.6: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	1 (8.33)	11 (91.67)	NC (NC, NC)	0.08	(0.00, 1.33)	0.141
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (58.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.20.1.6: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	5 (31.25)	11 (68.75)	NC (169.00, NC)	0.47	(0.09, 2.37)	0.649
	Placebo N=74	11	5 (45.45)	6 (54.55)	336.00 (220.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.20.1.6: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	6 (21.43)	22 (78.57)	NC (NC, NC)	0.41	(0.16, 1.06)	0.053
	Placebo N=74	32	15 (46.88)	17 (53.13)	351.00 (223.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.20.1.7: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	7 (25.00)	21 (75.00)	NC (NC, NC)	0.38	(0.14, 1.00)	0.031	0.166
	Placebo N=74	19	11 (57.89)	8 (42.11)	226.00 (112.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.7: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	23	7 (30.43)	16 (69.57)	NC (224.00, NC)	1.38	(0.47, 4.07)	0.687
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (330.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.7: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	2 (11.76)	15 (88.24)	NC (NC, NC)	0.35	(0.07, 1.61)	0.130
	Placebo N=74	30	10 (33.33)	20 (66.67)	NC (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.8: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	0.98	(0.12, 7.81)	0.506	0.213
	Placebo N=74	21	2 (9.52)	19 (90.48)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.8: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	13 (27.08)	35 (72.92)	NC (NC, NC)	0.50	(0.26, 0.98)	0.033
	Placebo N=74	53	26 (49.06)	27 (50.94)	336.00 (223.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (NC, NC)	0.60	(0.05, 7.08)	0.617	0.949
	Placebo N=74	13	2 (15.38)	11 (84.62)	NC (220.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (113.00, NC)	0.28	(0.03, 2.65)	0.216
	Placebo N=74	8	4 (50.00)	4 (50.00)	336.00 (169.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	7 (23.33)	23 (76.67)	NC (NC, NC)	0.62	(0.25, 1.57)	0.190
	Placebo N=74	30	13 (43.33)	17 (56.67)	351.00 (169.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.20.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 5 or 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	7 (33.33)	14 (66.67)	NC (169.00, NC)	0.67	(0.24, 1.85)	0.701
	Placebo N=74	23	9 (39.13)	14 (60.87)	NC (170.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 5 or 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.2.3 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verbesserung der Schmerzspitze – Sensitivitätsanalyse

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Table 17.23.1.1: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	17 (56.67)	13 (43.33)	169.00 (53.00, NC)	1.42	(0.73, 2.78)	0.154	0.241
	Placebo N=74	42	18 (42.86)	24 (57.14)	NC (161.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_tte_subgrp_5.sas Executed: 24MAR2025 15:50:20

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Table 17.23.1.1: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	20 (52.63)	18 (47.37)	333.00 (63.00, NC)	2.56	(1.12, 5.89)	0.019
	Placebo N=74	32	8 (25.00)	24 (75.00)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.2: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	18 (58.06)	13 (41.94)	176.00 (57.00, NC)	2.68	(1.25, 5.74)	0.011	0.134
	Placebo N=74	42	11 (26.19)	31 (73.81)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_tte_subgrp_5.sas Executed: 24MAR2025 15:50:21

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Table 17.23.1.2: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	19 (51.35)	18 (48.65)	333.00 (55.00, NC)	1.18	(0.58, 2.41)	0.473
	Placebo N=74	32	15 (46.88)	17 (53.13)	NC (161.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_tte_subgrp_5.sas Executed: 24MAR202
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Table 17.23.1.3: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	10 (50.00)	NC (57.00, NC)	2.63	(0.89, 7.78)	0.182	0.717
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (161.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.23.1.3: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	21 (55.26)	17 (44.74)	281.00 (57.00, NC)	1.88	(0.97, 3.62)	0.078
	Placebo N=74	43	16 (37.21)	27 (62.79)	NC (177.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.23.1.3: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (35.00, NC)	NC	(0.00, NC)	0.771
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (162.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.23.1.4: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	5 (100)	0 (0.00)	57.00 (30.00, NC)	3.79	(0.72, 20.01)	0.266	0.929
	Placebo N=74	9	5 (55.56)	4 (44.44)	284.00 (29.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.23.1.4: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	31 (51.67)	29 (48.33)	281.00 (112.00, NC)	2.10	(1.19, 3.73)	0.011
	Placebo N=74	63	19 (30.16)	44 (69.84)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.23.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	6 (66.67)	3 (33.33)	113.00 (34.00, NC)	NC	(NC, NC)	0.016	0.984
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	13 (50.00)	13 (50.00)	333.00 (55.00, NC)	1.54	(0.67, 3.53)	0.227
	Placebo N=74	27	10 (37.04)	17 (62.96)	NC (177.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	8 (47.06)	9 (52.94)	NC (57.00, NC)	2.14	(0.70, 6.58)	0.241
	Placebo N=74	21	6 (28.57)	15 (71.43)	NC (161.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.5: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	10 (62.50)	6 (37.50)	176.00 (30.00, NC)	1.27	(0.49, 3.26)	0.593
	Placebo N=74	20	10 (50.00)	10 (50.00)	284.00 (57.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (55.00, NC)	1.09	(0.31, 3.90)	0.968	0.311
	Placebo N=74	18	7 (38.89)	11 (61.11)	NC (113.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.23.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	12	8 (66.67)	4 (33.33)	113.00 (28.00, NC)	8.11	(1.50, 43.93)	0.016
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (226.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.23.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (57.00, NC)	9.14	(0.48, 175.3)	0.092
	Placebo N=74	11	1 (9.09)	10 (90.91)	NC (162.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.23.1.6: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	18 (64.29)	10 (35.71)	112.00 (56.00, 344.00)	1.47	(0.73, 2.94)	0.162
	Placebo N=74	32	15 (46.88)	17 (53.13)	284.00 (112.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.23.1.7: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	28	18 (64.29)	10 (35.71)	60.50 (51.00, NC)	2.45	(1.01, 5.95)	0.065	0.198
	Placebo N=74	19	7 (36.84)	12 (63.16)	NC (57.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.7: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	23	13 (56.52)	10 (43.48)	288.00 (57.00, NC)	2.53	(0.97, 6.64)	0.067
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (284.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.7: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (58.00, NC)	1.00	(0.37, 2.72)	0.808
	Placebo N=74	30	12 (40.00)	18 (60.00)	NC (118.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.8: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	10 (50.00)	113.00 (29.00, NC)	1.57	(0.62, 3.99)	0.282	0.926
	Placebo N=74	21	9 (42.86)	12 (57.14)	NC (113.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.8: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	27 (56.25)	21 (43.75)	281.00 (63.00, NC)	1.88	(1.02, 3.48)	0.027
	Placebo N=74	53	17 (32.08)	36 (67.92)	NC (284.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	4 (36.36)	113.00 (28.00, NC)	3.79	(0.85, 17.00)	0.159	0.492
	Placebo N=74	13	4 (30.77)	9 (69.23)	NC (30.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (57.00, NC)	0.64	(0.06, 7.16)	0.787
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (161.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	15 (50.00)	15 (50.00)	333.00 (55.00, NC)	1.32	(0.63, 2.78)	0.437
	Placebo N=74	30	13 (43.33)	17 (56.67)	NC (162.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.23.1.9: PGIC, Spikes of pain since last visit to study site - time to first improvement by reaching response 1 or 2 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	14 (66.67)	7 (33.33)	113.00 (53.00, NC)	2.81	(1.11, 7.10)	0.018
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (168.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement in spikes of pain since last visit to study site by reaching response 1 or 2.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.2.4 Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Zeit bis zur erstmaligen Verschlechterung der Schmerzspitze – Sensitivitätsanalyse

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Table 17.26.1.1: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	3 (10.00)	27 (90.00)	NC (NC, NC)	1.02	(0.23, 4.48)	0.809	0.451
	Placebo N=74	42	5 (11.90)	37 (88.10)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.1: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	4 (10.53)	34 (89.47)	NC (NC, NC)	0.54	(0.16, 1.90)	0.214
	Placebo N=74	32	7 (21.88)	25 (78.13)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.2: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	31	6 (19.35)	25 (80.65)	NC (NC, NC)	1.12	(0.38, 3.34)	0.686	0.293
	Placebo N=74	42	9 (21.43)	33 (78.57)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.2: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	37	1 (2.70)	36 (97.30)	NC (NC, NC)	0.24	(0.02, 2.44)	0.287
	Placebo N=74	32	3 (9.38)	29 (90.63)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.3: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	1 (5.00)	19 (95.00)	NC (NC, NC)	1.92	(0.10, 35.99)	0.959	0.822
	Placebo N=74	23	1 (4.35)	22 (95.65)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.26.1.3: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	38	5 (13.16)	33 (86.84)	NC (NC, NC)	0.59	(0.20, 1.74)	0.314
	Placebo N=74	43	10 (23.26)	33 (76.74)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.26.1.3: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	4	0 (0.00)	4 (100)	NC (NC, NC)	NC	(NC, NC)	0.371
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (56.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 17.26.1.4: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	0.169	0.996
	Placebo N=74	9	3 (33.33)	6 (66.67)	NC (28.00, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.26.1.4: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	60	7 (11.67)	53 (88.33)	NC (NC, NC)	0.89	(0.32, 2.45)	0.722
	Placebo N=74	63	9 (14.29)	54 (85.71)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.26.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	9	0 (0.00)	9 (100)	NC (NC, NC)	NC	(NC, NC)	NC	0.936
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	26	3 (11.54)	23 (88.46)	NC (NC, NC)	0.50	(0.13, 2.00)	0.230
	Placebo N=74	27	7 (25.93)	20 (74.07)	NC (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	17	1 (5.88)	16 (94.12)	NC (NC, NC)	1.92	(0.10, 35.99)	0.906
	Placebo N=74	21	1 (4.76)	20 (95.24)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.5: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	16	3 (18.75)	13 (81.25)	NC (274.00, NC)	0.64	(0.14, 2.97)	0.889
	Placebo N=74	20	4 (20.00)	16 (80.00)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.8: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	20	0 (0.00)	20 (100)	NC (NC, NC)	NC	(NC, NC)	0.357	0.994
	Placebo N=74	21	1 (4.76)	20 (95.24)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.8: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	48	7 (14.58)	41 (85.42)	NC (NC, NC)	0.67	(0.26, 1.74)	0.382
	Placebo N=74	53	11 (20.75)	42 (79.25)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	11	0 (0.00)	11 (100)	NC (NC, NC)	NC	(NC, NC)	NC	0.846
	Placebo N=74	13	0 (0.00)	13 (100)	NC (NC, NC)				

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (169.00, NC)	1.92	(0.10, 35.99)	0.788
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (281.00, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	30	4 (13.33)	26 (86.67)	NC (NC, NC)	0.70	(0.20, 2.43)	0.432
	Placebo N=74	30	7 (23.33)	23 (76.67)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.26.1.9: PGIC, Spikes of pain since last visit to study site - First Deterioration by reaching response 6 or 7 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIC - Spikes of pain, since last visit to study site	Selumetinib 25 mg/m2 BID N=71	21	2 (9.52)	19 (90.48)	NC (NC, NC)	0.36	(0.06, 2.08)	0.404
	Placebo N=74	23	4 (17.39)	19 (82.61)	NC (NC, NC)			

PGIC = Patients Global Impression of Change; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration in spikes of pain since last visit to study site by reaching response 6 or 7.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.3 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – chronischer Schmerz

1.1.5.3.1 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Verbesserung des chronischen Schmerzes zu Zyklus 12, Tag 28 – Hauptanalyse

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Table 17.71.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	10	7 (70.00)	2.00 (0.35, 11.36)	1.30 (0.68, 2.48)	0.16 (-0.23, 0.55)	0.669	0.996
Placebo N=74	13	7 (53.85)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.71.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	11	6 (54.55)	NC	NC	0.55 (0.25, 0.84)	0.012
Placebo N=74	10	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.71.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	8 (66.67)	NC	NC	0.67 (0.40, 0.93)	0.005
Placebo N=74	9	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.71.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	14 (58.33)	2.10 (0.67, 6.56)	1.46 (0.81, 2.62)	0.18 (-0.09, 0.46)	0.258
Placebo N=74	25	10 (40.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.71.1.7: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	16 (72.73)	8.89 (1.80, 43.82)	3.15 (1.13, 8.78)	0.50 (0.20, 0.79)	0.006	0.402
Placebo N=74	13	3 (23.08)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.7: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	12 (60.00)	4.00 (1.09, 14.62)	2.20 (1.02, 4.75)	0.33 (0.04, 0.61)	0.060
Placebo N=74	22	6 (27.27)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.7: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	15	7 (46.67)	1.64 (0.43, 6.19)	1.34 (0.62, 2.92)	0.12 (-0.20, 0.44)	0.514
Placebo N=74	23	8 (34.78)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.8: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	15	7 (46.67)	4.67 (0.95, 23.04)	2.96 (0.92, 9.53)	0.31 (0.01, 0.61)	0.068	0.471
Placebo N=74	19	3 (15.79)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.8: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	42	28 (66.67)	3.57 (1.43, 8.93)	1.86 (1.16, 2.97)	0.31 (0.10, 0.52)	0.008
Placebo N=74	39	14 (35.90)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	3.06 (0.54, 17.40)	1.75 (0.71, 4.31)	0.27 (-0.13, 0.67)	0.395	0.995
Placebo N=74	11	4 (36.36)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	6	2 (33.33)	NC	NC	0.33 (-0.04, 0.71)	0.165
Placebo N=74	8	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	23	15 (65.22)	3.48 (0.99, 12.24)	1.86 (0.96, 3.63)	0.30 (0.02, 0.59)	0.069
Placebo N=74	20	7 (35.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	11 (64.71)	3.97 (0.99, 15.91)	2.05 (0.97, 4.33)	0.33 (0.02, 0.64)	0.093
Placebo N=74	19	6 (31.58)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.1: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Age Group (Full Analysis Set)

Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	27	17 (62.96)	3.91 (1.33, 11.49)	2.08 (1.15, 3.76)	0.33 (0.09, 0.57)	0.018	0.947
Placebo N=74	33	10 (30.30)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.1: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Age Group (Full Analysis Set)

Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	18 (60.00)	3.86 (1.24, 12.04)	2.14 (1.07, 4.29)	0.32 (0.07, 0.57)	0.029
Placebo N=74	25	7 (28.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.2: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	31	18 (58.06)	5.54 (1.76, 17.39)	2.90 (1.34, 6.31)	0.38 (0.16, 0.61)	0.004	0.248
Placebo N=74	30	6 (20.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.2: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	26	17 (65.38)	2.92 (0.96, 8.84)	1.66 (0.97, 2.85)	0.26 (0.00, 0.52)	0.064
Placebo N=74	28	11 (39.29)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.3: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	4.00 (0.98, 16.27)	2.50 (0.94, 6.66)	0.30 (0.02, 0.58)	0.096	0.849
Placebo N=74	20	4 (20.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.71.1.3: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	28	19 (67.86)	3.65 (1.23, 10.81)	1.85 (1.08, 3.16)	0.31 (0.07, 0.56)	0.021
Placebo N=74	30	11 (36.67)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.71.1.3: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	4.00 (0.21, 75.66)	2.50 (0.34, 18.63)	0.30 (-0.30, 0.90)	0.524
Placebo N=74	5	1 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.71.1.4: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	2.00 (0.13, 31.98)	1.20 (0.59, 2.45)	0.13 (-0.38, 0.65)	1.000	0.117
Placebo N=74	6	4 (66.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.71.1.4: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	49	29 (59.18)	4.59 (1.94, 10.89)	2.47 (1.43, 4.25)	0.35 (0.17, 0.53)	0.001
Placebo N=74	50	12 (24.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.71.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	10.00 (0.65, 154.40)	4.00 (0.61, 26.12)	0.50 (0.02, 0.98)	0.242	0.252
Placebo N=74	6	1 (16.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	14 (70.00)	7.58 (1.74, 33.09)	2.97 (1.21, 7.34)	0.46 (0.18, 0.75)	0.008
Placebo N=74	17	4 (23.53)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	9 (52.94)	4.22 (0.98, 18.12)	2.51 (0.94, 6.70)	0.32 (0.02, 0.62)	0.082
Placebo N=74	19	4 (21.05)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.71.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	14	8 (57.14)	1.33 (0.32, 5.64)	1.14 (0.59, 2.23)	0.07 (-0.29, 0.43)	0.730
Placebo N=74	16	8 (50.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.3.2 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Verschlechterung des chronischen Schmerzes zu Zyklus 12, Tag 28 – Hauptanalyse

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Table 17.72.1.4: PGIC, chronic pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	NC	NC	-0.17 (-0.46, 0.13)	1.000	1.000
Placebo N=74	6	1 (16.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.72.1.4: PGIC, chronic pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	49	3 (6.12)	0.34 (0.09, 1.38)	0.38 (0.11, 1.36)	-0.10 (-0.22, 0.02)	0.200
Placebo N=74	50	8 (16.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.72.1.8: PGIC, chronic pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	15	0 (0.00)	NC	NC	-0.11 (-0.24, 0.03)	0.492	1.000
Placebo N=74	19	2 (10.53)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.72.1.8: PGIC, chronic pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	42	3 (7.14)	0.35 (0.08, 1.47)	0.40 (0.11, 1.43)	-0.11 (-0.25, 0.04)	0.184
Placebo N=74	39	7 (17.95)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.3.3 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Verbesserung des chronischen Schmerzes zu Zyklus 12, Tag 28 – Sensitivitätsanalyse

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Table 17.69.1.7: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	11 (50.00)	5.50 (0.98, 30.80)	3.25 (0.85, 12.43)	0.35 (0.06, 0.63)	0.070	0.555
Placebo N=74	13	2 (15.38)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.7: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	9 (45.00)	5.18 (1.15, 23.29)	3.30 (1.04, 10.50)	0.31 (0.05, 0.57)	0.040
Placebo N=74	22	3 (13.64)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.7: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	15	5 (33.33)	1.80 (0.42, 7.76)	1.53 (0.53, 4.40)	0.12 (-0.18, 0.41)	0.473
Placebo N=74	23	5 (21.74)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.8: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	15	5 (33.33)	2.67 (0.52, 13.68)	2.11 (0.60, 7.45)	0.18 (-0.11, 0.46)	0.417	0.760
Placebo N=74	19	3 (15.79)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.8: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	42	20 (47.62)	4.16 (1.50, 11.50)	2.65 (1.26, 5.57)	0.30 (0.10, 0.49)	0.005
Placebo N=74	39	7 (17.95)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	4 (36.36)	1.52 (0.25, 9.29)	1.33 (0.39, 4.62)	0.09 (-0.30, 0.48)	1.000	0.788
Placebo N=74	11	3 (27.27)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	NC	NC	0.17 (-0.13, 0.46)	0.429
Placebo N=74	8	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	23	10 (43.48)	4.36 (0.99, 19.12)	2.90 (0.92, 9.09)	0.28 (0.03, 0.54)	0.054
Placebo N=74	20	3 (15.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.9: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	10 (58.82)	5.36 (1.24, 23.21)	2.79 (1.07, 7.28)	0.38 (0.08, 0.67)	0.039
Placebo N=74	19	4 (21.05)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.1: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Age Group by Age Group (Full Analysis Set)

Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	27	13 (48.15)	5.20 (1.54, 17.52)	3.18 (1.30, 7.79)	0.33 (0.11, 0.55)	0.010	0.475
Placebo N=74	33	5 (15.15)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.1: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Age Group by Age Group (Full Analysis Set)

Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	2.67 (0.79, 9.05)	2.00 (0.81, 4.91)	0.20 (-0.04, 0.44)	0.147
Placebo N=74	25	5 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.2: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	31	15 (48.39)	8.44 (2.11, 33.72)	4.84 (1.56, 15.03)	0.38 (0.18, 0.59)	0.002	0.106
Placebo N=74	30	3 (10.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.2: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	26	10 (38.46)	1.88 (0.59, 6.01)	1.54 (0.69, 3.44)	0.13 (-0.11, 0.38)	0.382
Placebo N=74	28	7 (25.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.3: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	20	6 (30.00)	2.43 (0.51, 11.51)	2.00 (0.58, 6.91)	0.15 (-0.10, 0.40)	0.451	0.927
Placebo N=74	20	3 (15.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.69.1.3: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	4.62 (1.44, 14.76)	2.68 (1.21, 5.93)	0.34 (0.10, 0.57)	0.013
Placebo N=74	30	6 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.69.1.3: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	4	0 (0.00)	NC	NC	-0.20 (-0.55, 0.15)	1.000
Placebo N=74	5	1 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.69.1.4: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	4.00 (0.27, 60.32)	1.60 (0.64, 3.98)	0.30 (-0.23, 0.83)	0.545	0.199
Placebo N=74	6	3 (50.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.69.1.4: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	49	21 (42.86)	5.50 (1.98, 15.31)	3.57 (1.58, 8.09)	0.31 (0.14, 0.47)	0.001
Placebo N=74	50	6 (12.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.69.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	NC	NC	0.50 (0.10, 0.90)	0.182	0.400
Placebo N=74	6	0 (0.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	16.00 (1.77, 144.72)	8.50 (1.21, 59.82)	0.44 (0.20, 0.69)	0.004
Placebo N=74	17	1 (5.88)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	5 (29.41)	2.22 (0.44, 11.18)	1.86 (0.52, 6.65)	0.14 (-0.14, 0.41)	0.434
Placebo N=74	19	3 (15.79)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.5: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	14	7 (50.00)	1.67 (0.39, 7.15)	1.33 (0.59, 3.03)	0.13 (-0.23, 0.48)	0.713
Placebo N=74	16	6 (37.50)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.69.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	10	5 (50.00)	1.60 (0.30, 8.49)	1.30 (0.52, 3.28)	0.12 (-0.29, 0.52)	0.685	0.961
Placebo N=74	13	5 (38.46)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.69.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	11	6 (54.55)	NC	NC	0.55 (0.25, 0.84)	0.012
Placebo N=74	10	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.69.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	NC	NC	0.42 (0.14, 0.70)	0.045
Placebo N=74	9	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.69.1.6: PGIC, chronic pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	9 (37.50)	2.40 (0.67, 8.65)	1.88 (0.73, 4.79)	0.18 (-0.07, 0.42)	0.217
Placebo N=74	25	5 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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1.1.5.4 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Schmerzspitze

1.1.5.4.1 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Verbesserung der Schmerzspitze zu Zyklus 12, Tag 28 – Hauptanalyse

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Table 17.75.1.1: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Age Group (Full Analysis Set)

Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	27	15 (55.56)	2.19 (0.77, 6.18)	1.53 (0.87, 2.68)	0.19 (-0.06, 0.44)	0.193	0.253
Placebo N=74	33	12 (36.36)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.1: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Age Group (Full Analysis Set)

Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	19 (63.33)	5.47 (1.68, 17.81)	2.64 (1.25, 5.58)	0.39 (0.15, 0.63)	0.006
Placebo N=74	25	6 (24.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.2: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	31	19 (61.29)	7.92 (2.38, 26.33)	3.68 (1.58, 8.58)	0.45 (0.23, 0.66)	0.001	0.032
Placebo N=74	30	5 (16.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.2: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	26	15 (57.69)	1.57 (0.54, 4.61)	1.24 (0.74, 2.08)	0.11 (-0.15, 0.38)	0.430
Placebo N=74	28	13 (46.43)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.3: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	3.00 (0.79, 11.44)	2.00 (0.83, 4.81)	0.25 (-0.04, 0.54)	0.191	0.926
Placebo N=74	20	5 (25.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.75.1.3: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	28	18 (64.29)	3.11 (1.06, 9.08)	1.75 (1.02, 3.02)	0.28 (0.03, 0.52)	0.065
Placebo N=74	30	11 (36.67)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.75.1.3: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	4.00 (0.21, 75.66)	2.50 (0.34, 18.63)	0.30 (-0.30, 0.90)	0.524
Placebo N=74	5	1 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.75.1.4: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	5 (100.00)	NC	1.50 (0.85, 2.64)	0.33 (-0.04, 0.71)	0.455	0.333
Placebo N=74	6	4 (66.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.75.1.4: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	49	28 (57.14)	3.79 (1.62, 8.86)	2.20 (1.30, 3.72)	0.31 (0.13, 0.50)	0.002
Placebo N=74	50	13 (26.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.75.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	10.00 (0.65, 154.40)	4.00 (0.61, 26.12)	0.50 (0.02, 0.98)	0.242	0.493
Placebo N=74	6	1 (16.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	12 (60.00)	4.88 (1.16, 20.45)	2.55 (1.01, 6.45)	0.36 (0.07, 0.66)	0.045
Placebo N=74	17	4 (23.53)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	9 (52.94)	3.15 (0.78, 12.73)	2.01 (0.84, 4.83)	0.27 (-0.04, 0.58)	0.171
Placebo N=74	19	5 (26.32)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	14	9 (64.29)	1.80 (0.41, 7.81)	1.29 (0.69, 2.41)	0.14 (-0.21, 0.49)	0.484
Placebo N=74	16	8 (50.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	10	6 (60.00)	1.29 (0.24, 6.83)	1.11 (0.55, 2.27)	0.06 (-0.35, 0.47)	1.000	0.423
Placebo N=74	13	7 (53.85)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.75.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	15.75 (1.42, 174.25)	6.36 (0.94, 43.07)	0.54 (0.20, 0.88)	0.024
Placebo N=74	10	1 (10.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.75.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	8 (66.67)	NC	NC	0.67 (0.40, 0.93)	0.005
Placebo N=74	9	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.75.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	13 (54.17)	1.77 (0.57, 5.51)	1.35 (0.74, 2.48)	0.14 (-0.14, 0.42)	0.396
Placebo N=74	25	10 (40.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.75.1.7: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	14 (63.64)	5.83 (1.23, 27.63)	2.76 (0.97, 7.81)	0.41 (0.10, 0.71)	0.035	0.730
Placebo N=74	13	3 (23.08)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.7: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	11 (55.00)	2.62 (0.74, 9.21)	1.73 (0.83, 3.58)	0.23 (-0.06, 0.52)	0.212
Placebo N=74	22	7 (31.82)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.7: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	15	9 (60.00)	2.81 (0.73, 10.77)	1.73 (0.86, 3.46)	0.25 (-0.06, 0.57)	0.185
Placebo N=74	23	8 (34.78)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.8: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	15	8 (53.33)	2.48 (0.61, 10.06)	1.69 (0.75, 3.81)	0.22 (-0.11, 0.55)	0.296	0.723
Placebo N=74	19	6 (31.58)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.8: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	42	26 (61.90)	3.66 (1.45, 9.19)	2.01 (1.19, 3.41)	0.31 (0.11, 0.52)	0.007
Placebo N=74	39	12 (30.77)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	3.06 (0.54, 17.40)	1.75 (0.71, 4.31)	0.27 (-0.13, 0.67)	0.395	0.913
Placebo N=74	11	4 (36.36)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	6	2 (33.33)	3.50 (0.24, 51.90)	2.67 (0.31, 23.00)	0.21 (-0.23, 0.65)	0.538
Placebo N=74	8	1 (12.50)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	23	13 (56.52)	2.41 (0.70, 8.30)	1.61 (0.80, 3.24)	0.22 (-0.08, 0.51)	0.223
Placebo N=74	20	7 (35.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.75.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 or 3 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	12 (70.59)	5.20 (1.25, 21.57)	2.24 (1.08, 4.64)	0.39 (0.09, 0.69)	0.044
Placebo N=74	19	6 (31.58)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better) or 3 (A little better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.5.4.2 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Verschlechterung der Schmerzspitze zu Zyklus 12, Tag 28 – Hauptanalyse

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Table 17.76.1.2: PGIC, spike pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	31	3 (9.68)	0.35 (0.08, 1.52)	0.41 (0.12, 1.46)	-0.14 (-0.32, 0.05)	0.182	1.000
Placebo N=74	30	7 (23.33)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.76.1.2: PGIC, spike pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	26	0 (0.00)	NC	NC	-0.14 (-0.27, -0.01)	0.112
Placebo N=74	28	4 (14.29)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.76.1.4: PGIC, spike pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	NC	NC	-0.33 (-0.71, 0.04)	0.455	1.000
Placebo N=74	6	2 (33.33)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.76.1.4: PGIC, spike pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)

Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	49	3 (6.12)	0.30 (0.08, 1.17)	0.34 (0.10, 1.18)	-0.12 (-0.24, 0.01)	0.121
Placebo N=74	50	9 (18.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.76.1.8: PGIC, spike pain since starting the study medication - Patients with deterioration by reaching response 5 or 6 or 7 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	42	3 (7.14)	0.20 (0.05, 0.77)	0.25 (0.08, 0.84)	-0.21 (-0.37, -0.05)	0.018	NC#
Placebo N=74	39	11 (28.21)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Deterioration is defined as worsening in PGIC scale by reaching response 5 (A little worse) or 6 (Moderately worse) or 7 (Much worse).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factors with no events across both treatments have been excluded from the output.
P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
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1.1.5.4.3 Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Verbesserung der Schmerzspitze zu Zyklus 12, Tag 28 – Sensitivitätsanalyse

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Table 17.73.1.1: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Age Group (Full Analysis Set)
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	27	15 (55.56)	7.00 (2.07, 23.65)	3.67 (1.53, 8.80)	0.40 (0.18, 0.63)	0.002	0.343
Placebo N=74	33	5 (15.15)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.1: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Age Group (Full Analysis Set)
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	2.67 (0.79, 9.05)	2.00 (0.81, 4.91)	0.20 (-0.04, 0.44)	0.147
Placebo N=74	25	5 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.2: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	31	15 (48.39)	13.13 (2.65, 64.89)	7.26 (1.81, 29.06)	0.42 (0.22, 0.61)	0.000	0.059
Placebo N=74	30	2 (6.67)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.2: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Sex (Full Analysis Set)
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	26	12 (46.15)	2.14 (0.70, 6.60)	1.62 (0.79, 3.31)	0.18 (-0.08, 0.43)	0.260
Placebo N=74	28	8 (28.57)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.3: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	4.85 (0.86, 27.22)	3.50 (0.83, 14.83)	0.25 (0.00, 0.50)	0.127	0.759
Placebo N=74	20	2 (10.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.73.1.3: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	3.79 (1.23, 11.69)	2.30 (1.10, 4.79)	0.30 (0.06, 0.54)	0.030
Placebo N=74	30	7 (23.33)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.73.1.3: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Race (Full Analysis Set)
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	1.33 (0.06, 31.12)	1.25 (0.11, 14.34)	0.05 (-0.50, 0.60)	1.000
Placebo N=74	5	1 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from respective overall summary table.
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Table 17.73.1.4: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	5 (100.00)	NC	2.00 (0.90, 4.45)	0.50 (0.10, 0.90)	0.182	0.320
Placebo N=74	6	3 (50.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.73.1.4: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	49	21 (42.86)	5.50 (1.98, 15.31)	3.57 (1.58, 8.09)	0.31 (0.14, 0.47)	0.001
Placebo N=74	50	6 (12.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 17.73.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	NC	NC	0.50 (0.10, 0.90)	0.182	0.562
Placebo N=74	6	0 (0.00)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	10 (50.00)	7.50 (1.35, 41.72)	4.25 (1.08, 16.79)	0.38 (0.12, 0.65)	0.017
Placebo N=74	17	2 (11.76)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	4.64 (0.79, 27.24)	3.35 (0.78, 14.44)	0.25 (-0.02, 0.51)	0.114
Placebo N=74	19	2 (10.53)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.5: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Full Analysis Set)

Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	14	8 (57.14)	2.22 (0.51, 9.61)	1.52 (0.70, 3.32)	0.20 (-0.15, 0.55)	0.464
Placebo N=74	16	6 (37.50)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	10	3 (30.00)	0.69 (0.12, 3.96)	0.78 (0.24, 2.51)	-0.08 (-0.47, 0.30)	1.000	0.222
Placebo N=74	13	5 (38.46)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.73.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	15.75 (1.42, 174.25)	6.36 (0.94, 43.07)	0.54 (0.20, 0.88)	0.024
Placebo N=74	10	1 (10.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.73.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	NC	NC	0.50 (0.22, 0.78)	0.019
Placebo N=74	9	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.73.1.6: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Target PN Location (Full Analysis Set)

Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	11 (45.83)	4.44 (1.17, 16.92)	2.86 (1.06, 7.77)	0.30 (0.05, 0.54)	0.032
Placebo N=74	25	4 (16.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 17.73.1.7: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	12 (54.55)	6.60 (1.18, 37.03)	3.55 (0.94, 13.41)	0.39 (0.11, 0.68)	0.034	0.875
Placebo N=74	13	2 (15.38)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.7: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	20	9 (45.00)	3.68 (0.91, 14.88)	2.48 (0.90, 6.80)	0.27 (-0.00, 0.54)	0.096
Placebo N=74	22	4 (18.18)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.7: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	15	6 (40.00)	3.17 (0.71, 14.10)	2.30 (0.78, 6.81)	0.23 (-0.07, 0.52)	0.150
Placebo N=74	23	4 (17.39)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.8: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	15	7 (46.67)	4.67 (0.95, 23.04)	2.96 (0.92, 9.53)	0.31 (0.01, 0.61)	0.068	0.879
Placebo N=74	19	3 (15.79)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.8: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	42	20 (47.62)	4.16 (1.50, 11.50)	2.65 (1.26, 5.57)	0.30 (0.10, 0.49)	0.005
Placebo N=74	39	7 (17.95)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	5 (45.45)	3.75 (0.54, 26.04)	2.50 (0.61, 10.25)	0.27 (-0.10, 0.64)	0.361	0.997
Placebo N=74	11	2 (18.18)					

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	NC	NC	0.17 (-0.13, 0.46)	0.429
Placebo N=74	8	0 (0.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	23	11 (47.83)	3.67 (0.93, 14.39)	2.39 (0.90, 6.34)	0.28 (0.01, 0.55)	0.107
Placebo N=74	20	4 (20.00)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 17.73.1.9: PGIC, spike pain since starting the study medication - Patients with improvement by reaching response 1 or 2 at Cycle 12, Day 28 by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	10 (58.82)	5.36 (1.24, 23.21)	2.79 (1.07, 7.28)	0.38 (0.08, 0.67)	0.039
Placebo N=74	19	4 (21.05)				

PGIC = Patients Global Impression of Change; OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence interval
Improvement is defined as an improvement in PGIC scale by reaching response 1 (Much better) or 2 (Moderately better).
[a] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with Cycle 12, Day 28 response available
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.6 Endpunkt Schmerz anhand PGIS

1.1.6.1 Schmerz anhand PGIS – chronischer Schmerz

1.1.6.1.1 Schmerz anhand PGIS – Zeit bis zur erstmaligen Verbesserung des chronischen Schmerzes

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Table 18.5.1.9: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	11	4 (36.36)	7 (63.64)	NC (57.00, NC)	1.33	(0.28, 6.46)	0.726	0.792
	Placebo N=74	13	5 (38.46)	8 (61.54)	NC (30.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.9: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	2 (33.33)	57.00 (29.00, NC)	0.96	(0.25, 3.63)	0.730
	Placebo N=74	8	6 (75.00)	2 (25.00)	166.00 (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.9: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	30	22 (73.33)	8 (26.67)	111.00 (30.00, 168.00)	1.52	(0.81, 2.86)	0.360
	Placebo N=74	29	18 (62.07)	11 (37.93)	169.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.9: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	20	13 (65.00)	7 (35.00)	57.00 (29.00, NC)	2.07	(0.92, 4.68)	0.211
	Placebo N=74	22	12 (54.55)	10 (45.45)	265.00 (57.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.1: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	30	17 (56.67)	13 (43.33)	111.00 (53.00, NC)	2.03	(0.98, 4.22)	0.630	0.600
	Placebo N=74	40	23 (57.50)	17 (42.50)	226.00 (108.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.1: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	37	26 (70.27)	11 (29.73)	112.00 (57.00, 169.00)	1.45	(0.78, 2.67)	0.366
	Placebo N=74	32	18 (56.25)	14 (43.75)	162.00 (54.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.2: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	30	22 (73.33)	8 (26.67)	57.50 (30.00, 168.00)	1.69	(0.93, 3.07)	0.138	0.608
	Placebo N=74	42	24 (57.14)	18 (42.86)	226.00 (107.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.2: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	37	21 (56.76)	16 (43.24)	163.00 (57.00, NC)	1.35	(0.65, 2.80)	0.782
	Placebo N=74	30	17 (56.67)	13 (43.33)	172.00 (54.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.3: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	19	9 (47.37)	10 (52.63)	NC (57.00, NC)	1.19	(0.49, 2.91)	0.742	0.715
	Placebo N=74	23	13 (56.52)	10 (43.48)	175.00 (106.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.5.1.3: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	38	26 (68.42)	12 (31.58)	113.00 (57.00, 169.00)	1.53	(0.86, 2.71)	0.237
	Placebo N=74	41	23 (56.10)	18 (43.90)	226.00 (56.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.5.1.3: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	2 (50.00)	NC (30.00, NC)	19.7	(0.47, 831.1)	0.478
	Placebo N=74	5	4 (80.00)	1 (20.00)	162.00 (28.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.5.1.4: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	57.00 (29.00, NC)	1.32	(0.24, 7.32)	0.301	0.572
	Placebo N=74	8	7 (87.50)	1 (12.50)	57.00 (28.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.5.1.4: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	59	38 (64.41)	21 (35.59)	112.00 (57.00, 169.00)	1.61	(1.00, 2.60)	0.099
	Placebo N=74	62	32 (51.61)	30 (48.39)	232.00 (113.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.5.1.5: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	8	5 (62.50)	3 (37.50)	82.50 (25.00, NC)	9.58	(1.01, 91.25)	0.142	0.291
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (114.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.5: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	26	19 (73.08)	7 (26.92)	113.00 (35.00, 170.00)	1.48	(0.75, 2.91)	0.484
	Placebo N=74	26	16 (61.54)	10 (38.46)	169.00 (32.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.5: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	17	8 (47.06)	9 (52.94)	NC (57.00, NC)	1.18	(0.47, 3.00)	0.831
	Placebo N=74	21	11 (52.38)	10 (47.62)	175.00 (54.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.5: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	16	11 (68.75)	5 (31.25)	57.00 (29.00, 169.00)	1.24	(0.52, 2.97)	0.427
	Placebo N=74	19	12 (63.16)	7 (36.84)	113.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.6: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Comparison of treatment groups: Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	12	8 (66.67)	4 (33.33)	113.00 (29.00, NC)	0.61	(0.24, 1.56)	0.885	0.173
	Placebo N=74	18	12 (66.67)	6 (33.33)	107.00 (30.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.5.1.6: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	12	7 (58.33)	5 (41.67)	250.50 (28.00, NC)	1.86	(0.44, 7.98)	0.154
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (32.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.5.1.6: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	15	8 (53.33)	7 (46.67)	163.00 (55.00, NC)	1.29	(0.32, 5.20)	0.850
	Placebo N=74	11	6 (54.55)	5 (45.45)	288.00 (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.5.1.6: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	28	20 (71.43)	8 (28.57)	57.00 (29.00, 168.00)	2.62	(1.29, 5.31)	0.251
	Placebo N=74	30	18 (60.00)	12 (40.00)	173.00 (56.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.5.1.7: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	28	21 (75.00)	7 (25.00)	57.00 (30.00, 113.00)	1.66	(0.77, 3.60)	0.533	0.210
	Placebo N=74	18	11 (61.11)	7 (38.89)	81.50 (29.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.7: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	23	16 (69.57)	7 (30.43)	57.00 (29.00, 338.00)	1.64	(0.77, 3.47)	0.297
	Placebo N=74	25	15 (60.00)	10 (40.00)	175.00 (54.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.7: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (59.00, NC)	0.72	(0.27, 1.89)	0.430
	Placebo N=74	29	15 (51.72)	14 (48.28)	232.00 (108.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.8: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	20	6 (30.00)	14 (70.00)	NC (57.00, NC)	1.19	(0.30, 4.70)	0.370	0.811
	Placebo N=74	20	4 (20.00)	16 (80.00)	NC (NC, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.5.1.8: PGIS, Chronic Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	47	37 (78.72)	10 (21.28)	57.00 (35.00, 113.00)	1.52	(0.96, 2.43)	0.334
	Placebo N=74	52	37 (71.15)	15 (28.85)	113.00 (56.00, 226.00)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.6.1.2 Schmerz anhand PGIS – Zeit bis zur erstmaligen Verschlechterung des chronischen Schmerzes

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Table 18.2.1.6: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (51.00, NC)	1.31	(0.27, 6.47)	0.882	0.901
	Placebo N=74	18	4 (22.22)	14 (77.78)	NC (118.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.2.1.6: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	12	2 (16.67)	10 (83.33)	NC (169.00, NC)	1.23	(0.17, 8.81)	0.983
	Placebo N=74	12	2 (16.67)	10 (83.33)	NC (113.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.2.1.6: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	15	5 (33.33)	10 (66.67)	NC (169.00, NC)	0.65	(0.14, 2.96)	0.707
	Placebo N=74	11	4 (36.36)	7 (63.64)	NC (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.2.1.6: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	28	6 (21.43)	22 (78.57)	NC (NC, NC)	0.65	(0.22, 1.97)	0.590
	Placebo N=74	30	8 (26.67)	22 (73.33)	NC (330.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.2.1.7: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	28	9 (32.14)	19 (67.86)	NC (171.00, NC)	1.76	(0.46, 6.71)	0.314	0.333
	Placebo N=74	18	3 (16.67)	15 (83.33)	NC (280.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.7: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	23	4 (17.39)	19 (82.61)	NC (NC, NC)	0.67	(0.19, 2.38)	0.620
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.7: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	16	3 (18.75)	13 (81.25)	NC (229.00, NC)	0.49	(0.13, 1.88)	0.341
	Placebo N=74	29	9 (31.03)	20 (68.97)	NC (223.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.8: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (59.00, NC)	1.10	(0.36, 3.32)	0.854	0.500
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (113.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.8: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	47	9 (19.15)	38 (80.85)	NC (NC, NC)	0.77	(0.32, 1.89)	0.673
	Placebo N=74	52	11 (21.15)	41 (78.85)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.9: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	NC (171.00, NC)	0.64	(0.14, 2.90)	0.664	0.879
	Placebo N=74	13	4 (30.77)	9 (69.23)	NC (28.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.9: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	6	0 (0.00)	6 (100)	NC (NC, NC)	NC	(NC, NC)	0.386
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (223.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.9: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	30	6 (20.00)	24 (80.00)	NC (NC, NC)	0.91	(0.29, 2.83)	0.913
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.9: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (169.00, NC)	1.30	(0.45, 3.79)	0.775
	Placebo N=74	22	7 (31.82)	15 (68.18)	NC (280.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.1: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	30	9 (30.00)	21 (70.00)	NC (294.00, NC)	1.06	(0.43, 2.62)	0.871	0.947
	Placebo N=74	40	11 (27.50)	29 (72.50)	NC (NC, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.1: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	37	7 (18.92)	30 (81.08)	NC (NC, NC)	0.94	(0.33, 2.69)	0.766
	Placebo N=74	32	7 (21.88)	25 (78.13)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.2: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	30	6 (20.00)	24 (80.00)	NC (NC, NC)	0.36	(0.13, 0.95)	0.074	0.011
	Placebo N=74	42	15 (35.71)	27 (64.29)	NC (223.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.2: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	37	10 (27.03)	27 (72.97)	NC (NC, NC)	3.10	(0.81, 11.86)	0.066
	Placebo N=74	30	3 (10.00)	27 (90.00)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.3: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	19	4 (21.05)	15 (78.95)	NC (NC, NC)	0.67	(0.18, 2.50)	0.868	0.797
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.2.1.3: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	38	10 (26.32)	28 (73.68)	NC (NC, NC)	1.15	(0.48, 2.78)	0.834
	Placebo N=74	41	10 (24.39)	31 (75.61)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.2.1.3: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (282.00, NC)	NC	(0.00, NC)	0.665
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (280.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.2.1.4: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (30.00, NC)	0.07	(0.00, 10.01)	0.526	0.576
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (57.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.2.1.4: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	59	14 (23.73)	45 (76.27)	NC (NC, NC)	0.93	(0.45, 1.93)	0.878
	Placebo N=74	62	15 (24.19)	47 (75.81)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.2.1.5: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	8	4 (50.00)	4 (50.00)	294.00 (29.00, NC)	6.27	(0.59, 66.93)	0.187	0.362
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (30.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.5: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	26	6 (23.08)	20 (76.92)	NC (NC, NC)	0.91	(0.29, 2.85)	0.916
	Placebo N=74	26	6 (23.08)	20 (76.92)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.5: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	17	3 (17.65)	14 (82.35)	NC (NC, NC)	0.53	(0.12, 2.22)	0.555
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.2.1.5: PGIS, Chronic Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Chronic Pain	Selumetinib 25 mg/m2 BID N=71	16	3 (18.75)	13 (81.25)	NC (169.00, NC)	0.61	(0.15, 2.45)	0.402
	Placebo N=74	19	6 (31.58)	13 (68.42)	NC (280.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.6.2 Schmerz anhand PGIS – Schmerzspitze

1.1.6.2.1 Schmerz anhand PGIS – Zeit bis zur erstmaligen Verbesserung der Schmerzspitze

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Table 18.14.1.1: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	30	25 (83.33)	5 (16.67)	53.00 (29.00, 112.00)	2.01	(1.12, 3.61)	0.025	0.753
	Placebo N=74	40	25 (62.50)	15 (37.50)	113.50 (57.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.1: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	37	31 (83.78)	6 (16.22)	56.00 (29.00, 58.00)	1.88	(1.03, 3.43)	0.041
	Placebo N=74	32	18 (56.25)	14 (43.75)	113.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.2: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	30	27 (90.00)	3 (10.00)	54.00 (29.00, 112.00)	2.21	(1.25, 3.91)	0.006	0.619
	Placebo N=74	42	25 (59.52)	17 (40.48)	113.00 (38.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.2: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	37	29 (78.38)	8 (21.62)	56.00 (30.00, 111.00)	1.41	(0.71, 2.82)	0.106
	Placebo N=74	30	18 (60.00)	12 (40.00)	106.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.3: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	19	15 (78.95)	4 (21.05)	111.00 (29.00, 169.00)	2.51	(1.07, 5.87)	0.166	0.661
	Placebo N=74	23	13 (56.52)	10 (43.48)	161.00 (54.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.14.1.3: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	38	32 (84.21)	6 (15.79)	31.00 (29.00, 58.00)	1.96	(1.15, 3.36)	0.015
	Placebo N=74	41	24 (58.54)	17 (41.46)	113.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.14.1.3: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	4	3 (75.00)	1 (25.00)	57.00 (30.00, NC)	0.74	(0.08, 7.31)	0.611
	Placebo N=74	5	4 (80.00)	1 (20.00)	30.00 (28.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.14.1.4: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	5	5 (100)	0 (0.00)	29.00 (28.00, NC)	1.88	(0.50, 7.17)	0.321	0.644
	Placebo N=74	8	6 (75.00)	2 (25.00)	29.00 (28.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.14.1.4: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	59	49 (83.05)	10 (16.95)	55.00 (30.00, 111.00)	2.18	(1.39, 3.39)	0.001
	Placebo N=74	62	35 (56.45)	27 (43.55)	114.00 (57.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.14.1.5: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	8	6 (75.00)	2 (25.00)	41.00 (25.00, NC)	2.13	(0.55, 8.19)	0.375	0.996
	Placebo N=74	6	4 (66.67)	2 (33.33)	86.00 (38.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.5: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	26	23 (88.46)	3 (11.54)	43.00 (29.00, 112.00)	1.77	(0.93, 3.38)	0.073
	Placebo N=74	26	16 (61.54)	10 (38.46)	113.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.5: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	17	14 (82.35)	3 (17.65)	111.00 (29.00, 169.00)	2.35	(1.00, 5.53)	0.145
	Placebo N=74	21	12 (57.14)	9 (42.86)	161.00 (32.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.5: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	16	13 (81.25)	3 (18.75)	31.00 (29.00, 56.00)	1.49	(0.60, 3.67)	0.164
	Placebo N=74	19	11 (57.89)	8 (42.11)	113.00 (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.6: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	12	9 (75.00)	3 (25.00)	55.00 (28.00, 159.00)	1.01	(0.40, 2.53)	0.544	0.236
	Placebo N=74	18	11 (61.11)	7 (38.89)	57.00 (29.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.14.1.6: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	12	10 (83.33)	2 (16.67)	57.00 (28.00, NC)	2.58	(0.73, 9.06)	0.037
	Placebo N=74	12	5 (41.67)	7 (58.33)	NC (32.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.14.1.6: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	15	12 (80.00)	3 (20.00)	57.00 (30.00, 127.00)	6.29	(1.38, 28.61)	0.043
	Placebo N=74	11	5 (45.45)	6 (54.55)	NC (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.14.1.6: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	28	25 (89.29)	3 (10.71)	30.50 (29.00, 56.00)	2.11	(1.15, 3.89)	0.088
	Placebo N=74	30	21 (70.00)	9 (30.00)	57.00 (30.00, 115.00)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 18.14.1.7: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	28	26 (92.86)	2 (7.14)	30.50 (29.00, 57.00)	1.45	(0.73, 2.87)	0.295	0.593
	Placebo N=74	18	13 (72.22)	5 (27.78)	47.50 (29.00, 113.00)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.7: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	23	20 (86.96)	3 (13.04)	53.00 (29.00, 56.00)	2.31	(1.14, 4.66)	0.026
	Placebo N=74	25	16 (64.00)	9 (36.00)	113.00 (32.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.7: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	16	10 (62.50)	6 (37.50)	112.00 (56.00, NC)	1.74	(0.73, 4.16)	0.416
	Placebo N=74	29	14 (48.28)	15 (51.72)	NC (57.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.8: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	20	12 (60.00)	8 (40.00)	57.00 (29.00, NC)	2.46	(0.96, 6.34)	0.125	0.845
	Placebo N=74	20	9 (45.00)	11 (55.00)	NC (57.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.8: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	47	44 (93.62)	3 (6.38)	53.00 (29.00, 57.00)	2.25	(1.40, 3.61)	0.007
	Placebo N=74	52	34 (65.38)	18 (34.62)	58.00 (30.00, 169.00)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.9: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	11	10 (90.91)	1 (9.09)	111.00 (28.00, 113.00)	2.74	(0.92, 8.13)	0.124	0.970
	Placebo N=74	13	7 (53.85)	6 (46.15)	228.00 (30.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.9: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	2 (33.33)	127.00 (29.00, NC)	1.38	(0.34, 5.60)	0.949
	Placebo N=74	8	5 (62.50)	3 (37.50)	138.50 (28.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.9: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	30	26 (86.67)	4 (13.33)	31.00 (29.00, 58.00)	1.83	(0.99, 3.36)	0.055
	Placebo N=74	29	18 (62.07)	11 (37.93)	113.00 (30.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.14.1.9: PGIS, Spikes of Pain - Time to first decrease of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	20	16 (80.00)	4 (20.00)	53.00 (29.00, 57.00)	2.09	(0.97, 4.50)	0.064
	Placebo N=74	22	13 (59.09)	9 (40.91)	113.00 (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first decrease of pain is time from randomisation to first decrease by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.6.2.2 Schmerz anhand PGIS – Zeit bis zur erstmaligen Verschlechterung der Schmerzspitze

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Table 18.11.1.1: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	30	4 (13.33)	26 (86.67)	NC (NC, NC)	0.67	(0.20, 2.21)	0.313	0.764
	Placebo N=74	40	10 (25.00)	30 (75.00)	NC (339.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.1: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	37	5 (13.51)	32 (86.49)	NC (NC, NC)	0.49	(0.16, 1.48)	0.178
	Placebo N=74	32	9 (28.13)	23 (71.88)	NC (331.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.2: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	30	3 (10.00)	27 (90.00)	NC (NC, NC)	0.32	(0.09, 1.16)	0.050	0.324
	Placebo N=74	42	12 (28.57)	30 (71.43)	NC (339.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.2: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	37	6 (16.22)	31 (83.78)	NC (NC, NC)	0.77	(0.25, 2.41)	0.654
	Placebo N=74	30	7 (23.33)	23 (76.67)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.3: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	19	3 (15.79)	16 (84.21)	NC (NC, NC)	0.84	(0.19, 3.80)	0.672	0.862
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.11.1.3: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	38	5 (13.16)	33 (86.84)	NC (NC, NC)	0.48	(0.17, 1.38)	0.144
	Placebo N=74	41	12 (29.27)	29 (70.73)	NC (339.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.11.1.3: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (29.00, NC)	NC	(0.00, NC)	0.700
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (29.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 18.11.1.4: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	0.141	0.988
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (29.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.11.1.4: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	59	8 (13.56)	51 (86.44)	NC (NC, NC)	0.61	(0.26, 1.44)	0.145
	Placebo N=74	62	16 (25.81)	46 (74.19)	NC (339.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 18.11.1.5: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	8	2 (25.00)	6 (75.00)	NC (29.00, NC)	NC	(NC, NC)	0.202	0.831
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.5: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	26	4 (15.38)	22 (84.62)	NC (NC, NC)	0.53	(0.15, 1.82)	0.392
	Placebo N=74	26	7 (26.92)	19 (73.08)	NC (331.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.5: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	17	2 (11.76)	15 (88.24)	NC (NC, NC)	0.64	(0.12, 3.39)	0.373
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (274.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.5: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	16	1 (6.25)	15 (93.75)	NC (NC, NC)	0.16	(0.02, 1.28)	0.046
	Placebo N=74	19	7 (36.84)	12 (63.16)	NC (57.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.7: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	28	3 (10.71)	25 (89.29)	NC (NC, NC)	0.68	(0.14, 3.38)	0.542	0.993
	Placebo N=74	18	3 (16.67)	15 (83.33)	NC (NC, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.7: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	23	3 (13.04)	20 (86.96)	NC (NC, NC)	0.53	(0.13, 2.10)	0.254
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (339.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.7: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	16	3 (18.75)	13 (81.25)	NC (NC, NC)	0.54	(0.14, 2.05)	0.528
	Placebo N=74	29	9 (31.03)	20 (68.97)	NC (331.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.8: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	20	6 (30.00)	14 (70.00)	NC (59.00, NC)	0.80	(0.27, 2.36)	0.681	0.204
	Placebo N=74	20	9 (45.00)	11 (55.00)	339.00 (118.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.8: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	47	3 (6.38)	44 (93.62)	NC (NC, NC)	0.30	(0.08, 1.09)	0.064
	Placebo N=74	52	10 (19.23)	42 (80.77)	NC (NC, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.9: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (NC, NC)	0.84	(0.06, 11.71)	0.636	1.000
	Placebo N=74	13	2 (15.38)	11 (84.62)	NC (169.00, NC)				

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.9: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (29.00, NC)	0.48	(0.05, 4.68)	0.498
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (109.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.9: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	30	4 (13.33)	26 (86.67)	NC (NC, NC)	0.55	(0.16, 1.88)	0.386
	Placebo N=74	29	7 (24.14)	22 (75.86)	NC (331.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 18.11.1.9: PGIS, Spikes of Pain - Time to first increase of pain by >=1 category on a 4-point scale by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PGIS, Spikes of Pain	Selumetinib 25 mg/m2 BID N=71	20	3 (15.00)	17 (85.00)	NC (NC, NC)	0.50	(0.13, 1.95)	0.219
	Placebo N=74	22	7 (31.82)	15 (68.18)	NC (118.00, NC)			

PGIS = Patient Global Impression of Severity; CI = Confidence interval
Time to first increase of pain is time from randomisation to first increase by at least 1 category on a 4-point scale, ie 1 = No pain to 4 = Severe, compared with the baseline score. Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.7 Endpunkt Schmerz anhand der Schmerzmedikation

1.1.7.1 Schmerz anhand der Schmerzmedikation – Zeit bis zum erstmaligen Anstieg der PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch um ≥ 0,5 Punkte

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Table 8.23.1.3: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	22	2 (9.09)	20 (90.91)	NC (NC, NC)	0.27	(0.04, 2.10)	0.169	0.968
	Placebo N=74	23	6 (26.09)	17 (73.91)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.3: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	38	4 (10.53)	34 (89.47)	NC (NC, NC)	0.54	(0.16, 1.84)	0.415
	Placebo N=74	41	7 (17.07)	34 (82.93)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.3: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	0.317
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (28.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.4: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	0.260	0.991
	Placebo N=74	9	2 (22.22)	7 (77.78)	NC (28.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.4: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	63	6 (9.52)	57 (90.48)	NC (NC, NC)	0.53	(0.20, 1.44)	0.125
	Placebo N=74	60	12 (20.00)	48 (80.00)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.5: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	9	0 (0.00)	9 (100)	NC (NC, NC)	NC	(NC, NC)	0.180	1.000
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (28.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.5: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	27	4 (14.81)	23 (85.19)	NC (NC, NC)	0.65	(0.18, 2.34)	0.425
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.5: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	18	2 (11.11)	16 (88.89)	NC (NC, NC)	0.77	(0.13, 4.40)	0.345
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.5: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	17	0 (0.00)	17 (100)	NC (NC, NC)	NC	(NC, NC)	0.196
	Placebo N=74	20	2 (10.00)	18 (90.00)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.6: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	13	2 (15.38)	11 (84.62)	NC (56.00, NC)	NC	(NC, NC)	0.092	0.466
	Placebo N=74	17	0 (0.00)	17 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.6: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	12	1 (8.33)	11 (91.67)	NC (NC, NC)	NC	(0.00, NC)	1.000
	Placebo N=74	12	1 (8.33)	11 (91.67)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.6: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	16	2 (12.50)	14 (87.50)	NC (NC, NC)	0.51	(0.06, 4.70)	0.173
	Placebo N=74	11	4 (36.36)	7 (63.64)	NC (168.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.6: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	30	1 (3.33)	29 (96.67)	NC (NC, NC)	0.07	(0.01, 0.58)	0.007
	Placebo N=74	30	9 (30.00)	21 (70.00)	NC (224.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.8: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	21	0 (0.00)	21 (100)	NC (NC, NC)	NC	(NC, NC)	0.329	0.991
	Placebo N=74	21	1 (4.76)	20 (95.24)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.8: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	50	6 (12.00)	44 (88.00)	NC (NC, NC)	0.47	(0.18, 1.26)	0.079
	Placebo N=74	50	13 (26.00)	37 (74.00)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.9: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	11	0 (0.00)	11 (100)	NC (NC, NC)	NC	(NC, NC)	0.358	0.997
	Placebo N=74	13	1 (7.69)	12 (92.31)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.9: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	7	2 (28.57)	5 (71.43)	NC (56.00, NC)	0.86	(0.15, 5.06)	0.594
	Placebo N=74	8	4 (50.00)	4 (50.00)	NC (56.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.9: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	31	4 (12.90)	27 (87.10)	NC (NC, NC)	0.61	(0.17, 2.15)	0.411
	Placebo N=74	28	6 (21.43)	22 (78.57)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.9: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	22	0 (0.00)	22 (100)	NC (NC, NC)	NC	(NC, NC)	0.076
	Placebo N=74	22	3 (13.64)	19 (86.36)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.1: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	32	2 (6.25)	30 (93.75)	NC (NC, NC)	0.27	(0.06, 1.32)	0.077	0.581
	Placebo N=74	40	9 (22.50)	31 (77.50)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.1: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	39	4 (10.26)	35 (89.74)	NC (NC, NC)	0.45	(0.11, 1.76)	0.459
	Placebo N=74	31	5 (16.13)	26 (83.87)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.2: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	33	3 (9.09)	30 (90.91)	NC (NC, NC)	0.32	(0.09, 1.16)	0.051	0.306
	Placebo N=74	39	11 (28.21)	28 (71.79)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.23.1.2: Pain Medication, Chronic Pain - Time to first increase in pain medication score using e-diary by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	38	3 (7.89)	35 (92.11)	NC (NC, NC)	0.74	(0.14, 3.92)	0.850
	Placebo N=74	32	3 (9.38)	29 (90.63)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase (by 0.5 points or at least 1 point) in pain medication score compared with the baseline score is achieved.
Subjects with no increase are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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1.1.7.2 Schmerz anhand der Schmerzmedikation – Zeit bis zur erstmaligen Abnahme der PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch um ≥ 1 Punkt

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Table 8.7.1.4: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	140.00 (28.00, NC)	2.05	(0.33, 12.79)	0.321	0.632
	Placebo N=74	9	3 (33.33)	6 (66.67)	NC (84.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.4: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	63	20 (31.75)	43 (68.25)	NC (NC, NC)	1.81	(0.88, 3.74)	0.081
	Placebo N=74	60	12 (20.00)	48 (80.00)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.5: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	9	6 (66.67)	3 (33.33)	84.00 (28.00, NC)	7.66	(0.66, 89.05)	0.046	0.625
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (336.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.5: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	27	11 (40.74)	16 (59.26)	NC (84.00, NC)	1.74	(0.67, 4.51)	0.291
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (308.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.5: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	18	2 (11.11)	16 (88.89)	NC (NC, NC)	1.00	(0.16, 6.10)	0.785
	Placebo N=74	21	3 (14.29)	18 (85.71)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.5: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	17	5 (29.41)	12 (70.59)	NC (84.00, NC)	1.34	(0.38, 4.70)	0.623
	Placebo N=74	20	5 (25.00)	15 (75.00)	NC (364.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.6: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	13	4 (30.77)	9 (69.23)	NC (84.00, NC)	1.76	(0.40, 7.69)	0.545	0.843
	Placebo N=74	17	4 (23.53)	13 (76.47)	NC (85.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.6: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (28.00, NC)	3.48	(0.58, 20.75)	0.392
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (252.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.6: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (31.00, NC)	3.71	(0.31, 45.14)	0.263
	Placebo N=74	11	2 (18.18)	9 (81.82)	NC (308.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.6: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	30	9 (30.00)	21 (70.00)	NC (337.00, NC)	1.78	(0.65, 4.87)	0.446
	Placebo N=74	30	7 (23.33)	23 (76.67)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.7: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	29	15 (51.72)	14 (48.28)	145.00 (84.00, NC)	4.12	(1.33, 12.76)	0.023	0.205
	Placebo N=74	19	4 (21.05)	15 (78.95)	NC (336.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.7: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	24	5 (20.83)	19 (79.17)	NC (NC, NC)	1.13	(0.30, 4.26)	0.778
	Placebo N=74	23	4 (17.39)	19 (82.61)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.7: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	18	4 (22.22)	14 (77.78)	NC (NC, NC)	0.81	(0.23, 2.88)	0.866
	Placebo N=74	29	8 (27.59)	21 (72.41)	NC (364.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.8: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	21	4 (19.05)	17 (80.95)	NC (NC, NC)	1.28	(0.20, 8.14)	0.349	0.822
	Placebo N=74	21	2 (9.52)	19 (90.48)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.8: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	50	20 (40.00)	30 (60.00)	NC (140.00, NC)	1.92	(0.96, 3.84)	0.145
	Placebo N=74	50	14 (28.00)	36 (72.00)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.9: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	11	0 (0.00)	11 (100)	NC (NC, NC)	NC	(NC, NC)	0.358	0.988
	Placebo N=74	13	1 (7.69)	12 (92.31)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.9: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	7	2 (28.57)	5 (71.43)	NC (84.00, NC)	1.59	(0.22, 11.35)	0.646
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (112.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.9: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	31	12 (38.71)	19 (61.29)	NC (84.00, NC)	1.85	(0.73, 4.71)	0.210
	Placebo N=74	28	7 (25.00)	21 (75.00)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.9: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	22	10 (45.45)	12 (54.55)	NC (84.00, NC)	2.03	(0.73, 5.67)	0.126
	Placebo N=74	22	6 (27.27)	16 (72.73)	NC (364.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.1: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	32	12 (37.50)	20 (62.50)	NC (84.00, NC)	2.93	(1.17, 7.34)	0.128	0.543
	Placebo N=74	40	10 (25.00)	30 (75.00)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.1: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	39	12 (30.77)	27 (69.23)	NC (337.00, NC)	1.84	(0.68, 4.94)	0.264
	Placebo N=74	31	6 (19.35)	25 (80.65)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.2: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	33	9 (27.27)	24 (72.73)	NC (NC, NC)	5.85	(1.23, 27.76)	0.008	0.046
	Placebo N=74	39	2 (5.13)	37 (94.87)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.2: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	38	15 (39.47)	23 (60.53)	NC (112.00, NC)	1.03	(0.48, 2.19)	0.899
	Placebo N=74	32	14 (43.75)	18 (56.25)	NC (196.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.3: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	22	4 (18.18)	18 (81.82)	NC (NC, NC)	1.22	(0.29, 5.16)	0.838	0.891
	Placebo N=74	23	4 (17.39)	19 (82.61)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.3: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	38	14 (36.84)	24 (63.16)	NC (145.00, NC)	1.74	(0.77, 3.92)	0.171
	Placebo N=74	41	10 (24.39)	31 (75.61)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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Table 8.7.1.3: Pain Medication, Chronic Pain - Time to first decrease in pain medication score by >= 1 point by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication e-Diary Assessment	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (84.00, NC)	0.32	(0.01, 12.66)	0.937
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (29.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease by at least 1 point compared with the baseline score is achieved.
Subjects with no decrease are censored at the expected last day of last cycle available during randomised period with non-missing pain medication details.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
All medication records during randomised period are considered (records that are in randomised period but are mapped to visit beyond cycle 12 are also considered).
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1.1.7.3 Schmerz anhand der Schmerzmedikation – Zeit bis zur erstmaligen Abnahme der Schmerzmedikation basierend auf der Bewertung des Prüfarztes

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Table 8.31.1.1: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	12 (40.00)	18 (60.00)	NC (59.00, NC)	4.27	(1.56, 11.66)	0.022	0.176
	Placebo N=74	41	7 (17.07)	34 (82.93)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.1: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	9 (23.68)	29 (76.32)	NC (NC, NC)	1.74	(0.57, 5.39)	0.477
	Placebo N=74	31	5 (16.13)	26 (83.87)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.2: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	31	11 (35.48)	20 (64.52)	NC (281.00, NC)	2.40	(0.89, 6.46)	0.103	0.633
	Placebo N=74	40	7 (17.50)	33 (82.50)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.2: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	37	10 (27.03)	27 (72.97)	NC (NC, NC)	1.58	(0.54, 4.63)	0.229
	Placebo N=74	32	5 (15.63)	27 (84.38)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.3: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	2 (10.00)	18 (90.00)	NC (NC, NC)	NC	(NC, NC)	0.133	1.000
	Placebo N=74	23	0 (0.00)	23 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.31.1.3: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	13 (34.21)	25 (65.79)	NC (281.00, NC)	1.11	(0.50, 2.47)	0.595
	Placebo N=74	41	12 (29.27)	29 (70.73)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.31.1.3: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (141.00, NC)	NC	(NC, NC)	0.264
	Placebo N=74	5	0 (0.00)	5 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.31.1.4: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	1 (20.00)	109.00 (57.00, NC)	1.17	(0.32, 4.26)	0.774	0.200
	Placebo N=74	9	6 (66.67)	3 (33.33)	29.00 (28.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.31.1.4: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	60	16 (26.67)	44 (73.33)	NC (NC, NC)	3.05	(1.19, 7.86)	0.011
	Placebo N=74	61	6 (9.84)	55 (90.16)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.31.1.5: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	5 (55.56)	NC (25.00, NC)	3.39	(0.37, 31.20)	0.225	0.715
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (114.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.5: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	26	8 (30.77)	18 (69.23)	NC (337.00, NC)	2.92	(0.77, 11.10)	0.091
	Placebo N=74	25	3 (12.00)	22 (88.00)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.5: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	1 (5.88)	16 (94.12)	NC (NC, NC)	NC	(NC, NC)	0.278
	Placebo N=74	21	0 (0.00)	21 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.5: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	8 (50.00)	113.00 (57.00, NC)	1.17	(0.42, 3.28)	0.494
	Placebo N=74	20	8 (40.00)	12 (60.00)	NC (29.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.6: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	2 (16.67)	10 (83.33)	NC (281.00, NC)	0.39	(0.04, 3.85)	0.971	0.710
	Placebo N=74	17	3 (17.65)	14 (82.35)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.31.1.6: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (29.00, NC)	2.85	(0.52, 15.60)	0.435
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (114.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.31.1.6: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	2 (12.50)	14 (87.50)	NC (NC, NC)	NC	(NC, NC)	0.225
	Placebo N=74	11	0 (0.00)	11 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.31.1.6: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	12 (42.86)	16 (57.14)	NC (86.00, NC)	2.41	(0.90, 6.46)	0.064
	Placebo N=74	31	6 (19.35)	25 (80.65)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.31.1.7: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	13 (46.43)	15 (53.57)	NC (85.00, NC)	3.94	(1.11, 13.94)	0.042	0.260
	Placebo N=74	19	3 (15.79)	16 (84.21)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.7: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	23	5 (21.74)	18 (78.26)	NC (337.00, NC)	1.24	(0.33, 4.64)	0.705
	Placebo N=74	24	4 (16.67)	20 (83.33)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.7: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	3 (17.65)	14 (82.35)	NC (NC, NC)	1.13	(0.24, 5.33)	0.896
	Placebo N=74	29	5 (17.24)	24 (82.76)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.8: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (109.00, NC)	4.29	(0.84, 21.82)	0.025	0.185
	Placebo N=74	21	2 (9.52)	19 (90.48)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.8: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	48	14 (29.17)	34 (70.83)	NC (NC, NC)	1.53	(0.68, 3.46)	0.294
	Placebo N=74	51	10 (19.61)	41 (80.39)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.9: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (NC, NC)	NC	(NC, NC)	0.296	0.727
	Placebo N=74	13	0 (0.00)	13 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.9: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	6	0 (0.00)	6 (100)	NC (NC, NC)	NC	(NC, NC)	NC
	Placebo N=74	8	0 (0.00)	8 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.9: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	9 (30.00)	21 (70.00)	NC (337.00, NC)	3.33	(0.90, 12.31)	0.053
	Placebo N=74	28	3 (10.71)	25 (89.29)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.31.1.9: Pain Medication - Time to first decrease in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	21	11 (52.38)	10 (47.62)	281.00 (81.00, NC)	1.26	(0.51, 3.16)	0.362
	Placebo N=74	23	9 (39.13)	14 (60.87)	NC (114.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.7.4 Schmerz anhand der Schmerzmedikation – Zeit bis zum erstmaligen Anstieg der Schmerzmedikation basierend auf der Bewertung des Prüfarztes

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Table 8.28.1.6: Pain Medication - Time to first increase in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (240.00, NC)	0.65	(0.12, 3.58)	0.983	0.622
	Placebo N=74	17	4 (23.53)	13 (76.47)	NC (204.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.28.1.6: Pain Medication - Time to first increase in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7 (58.33)	NC (84.00, NC)	1.25	(0.33, 4.83)	0.777
	Placebo N=74	12	5 (41.67)	7 (58.33)	NC (106.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.28.1.6: Pain Medication - Time to first increase in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	3 (18.75)	13 (81.25)	NC (222.00, NC)	0.11	(0.01, 1.24)	0.321
	Placebo N=74	11	4 (36.36)	7 (63.64)	NC (113.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.28.1.6: Pain Medication - Time to first increase in pain medication using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	7 (25.00)	21 (75.00)	NC (343.00, NC)	0.51	(0.20, 1.34)	0.262
	Placebo N=74	31	11 (35.48)	20 (64.52)	NC (200.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.28.1.7: Pain Medication - Time to first increase in pain medication using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	8 (28.57)	20 (71.43)	343.00 (343.00, NC)	0.93	(0.32, 2.72)	0.631	0.914
	Placebo N=74	19	6 (31.58)	13 (68.42)	NC (303.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.7: Pain Medication - Time to first increase in pain medication using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	23	6 (26.09)	17 (73.91)	NC (337.00, NC)	0.71	(0.24, 2.08)	0.583
	Placebo N=74	24	8 (33.33)	16 (66.67)	NC (200.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.7: Pain Medication - Time to first increase in pain medication using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	4 (23.53)	13 (76.47)	NC (253.00, NC)	0.65	(0.20, 2.12)	0.519
	Placebo N=74	29	10 (34.48)	19 (65.52)	NC (253.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.8: Pain Medication - Time to first increase in pain medication using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	4 (20.00)	16 (80.00)	343.00 (NC, NC)	0.63	(0.15, 2.56)	0.411	0.943
	Placebo N=74	21	6 (28.57)	15 (71.43)	NC (199.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.8: Pain Medication - Time to first increase in pain medication using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)

Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	48	14 (29.17)	34 (70.83)	NC (NC, NC)	0.80	(0.39, 1.61)	0.433
	Placebo N=74	51	18 (35.29)	33 (64.71)	NC (309.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.9: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (NC, NC)	1.46	(0.09, 24.93)	0.924	0.834
	Placebo N=74	13	1 (7.69)	12 (92.31)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.9: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (222.00, NC)	0.28	(0.03, 2.95)	0.396
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (29.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.9: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	8 (26.67)	22 (73.33)	NC (337.00, NC)	0.93	(0.35, 2.49)	0.896
	Placebo N=74	28	8 (28.57)	20 (71.43)	NC (313.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.9: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	21	8 (38.10)	13 (61.90)	NC (169.00, NC)	0.65	(0.26, 1.62)	0.423
	Placebo N=74	23	12 (52.17)	11 (47.83)	303.00 (136.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.1: Pain Medication - Time to first increase in pain medication using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	10 (33.33)	20 (66.67)	NC (240.00, NC)	1.38	(0.59, 3.22)	0.571	0.046
	Placebo N=74	41	12 (29.27)	29 (70.73)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.1: Pain Medication - Time to first increase in pain medication using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	8 (21.05)	30 (78.95)	NC (343.00, NC)	0.36	(0.14, 0.91)	0.050
	Placebo N=74	31	12 (38.71)	19 (61.29)	NC (200.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.2: Pain Medication - Time to first increase in pain medication using the investigator assessment by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	31	11 (35.48)	20 (64.52)	NC (253.00, NC)	1.06	(0.45, 2.50)	0.855	0.191
	Placebo N=74	40	12 (30.00)	28 (70.00)	NC (313.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.2: Pain Medication - Time to first increase in pain medication using the investigator assessment by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	37	7 (18.92)	30 (81.08)	NC (343.00, NC)	0.48	(0.19, 1.23)	0.118
	Placebo N=74	32	12 (37.50)	20 (62.50)	NC (253.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.3: Pain Medication - Time to first increase in pain medication using the investigator assessment by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	2 (10.00)	18 (90.00)	NC (NC, NC)	0.29	(0.05, 1.74)	0.147	0.235
	Placebo N=74	23	6 (26.09)	17 (73.91)	NC (313.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.28.1.3: Pain Medication - Time to first increase in pain medication using the investigator assessment by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	10 (26.32)	28 (73.68)	NC (343.00, NC)	0.67	(0.30, 1.51)	0.351
	Placebo N=74	41	15 (36.59)	26 (63.41)	NC (253.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.28.1.3: Pain Medication - Time to first increase in pain medication using the investigator assessment by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	2 (50.00)	NC (30.00, NC)	NC	(0.00, NC)	0.799
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (112.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.28.1.4: Pain Medication - Time to first increase in pain medication using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	3 (60.00)	NC (84.00, NC)	0.67	(0.13, 3.38)	0.369	0.723
	Placebo N=74	9	6 (66.67)	3 (33.33)	253.00 (56.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.28.1.4: Pain Medication - Time to first increase in pain medication using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	60	14 (23.33)	46 (76.67)	NC (343.00, NC)	0.71	(0.35, 1.43)	0.407
	Placebo N=74	61	18 (29.51)	43 (70.49)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.28.1.5: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	9	2 (22.22)	7 (77.78)	NC (191.00, NC)	0.78	(0.11, 5.69)	0.762	0.904
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (58.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.5: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	26	6 (23.08)	20 (76.92)	NC (343.00, NC)	0.68	(0.23, 1.98)	0.514
	Placebo N=74	25	8 (32.00)	17 (68.00)	NC (253.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.5: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	2 (11.76)	15 (88.24)	NC (NC, NC)	0.55	(0.10, 3.00)	0.476
	Placebo N=74	21	4 (19.05)	17 (80.95)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.28.1.5: Pain Medication - Time to first increase in pain medication using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	8 (50.00)	337.00 (86.00, NC)	0.91	(0.34, 2.41)	0.942
	Placebo N=74	20	10 (50.00)	10 (50.00)	303.00 (136.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.7.5 Schmerz anhand der Schmerzmedikation – Zeit bis zur erstmaligen Abnahme der Schmerzmedikation aufgrund von PN Schmerz basierend auf der Bewertung des Prüfarztes

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Table 8.13.1.5: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	5 (55.56)	NC (25.00, NC)	3.39	(0.37, 31.20)	0.225	0.517
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (114.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.5: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	26	8 (30.77)	18 (69.23)	NC (337.00, NC)	2.92	(0.77, 11.10)	0.091
	Placebo N=74	25	3 (12.00)	22 (88.00)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.5: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	1 (5.88)	16 (94.12)	NC (NC, NC)	NC	(NC, NC)	0.278
	Placebo N=74	21	0 (0.00)	21 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.5: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	10 (62.50)	NC (57.00, NC)	0.79	(0.25, 2.50)	0.884
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (29.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.6: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	2 (16.67)	10 (83.33)	NC (281.00, NC)	0.51	(0.04, 6.28)	0.701	0.908
	Placebo N=74	17	2 (11.76)	15 (88.24)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.13.1.6: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	4 (33.33)	8 (66.67)	NC (29.00, NC)	1.41	(0.26, 7.67)	0.740
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (114.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.13.1.6: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	2 (12.50)	14 (87.50)	NC (NC, NC)	NC	(NC, NC)	0.225
	Placebo N=74	11	0 (0.00)	11 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.13.1.6: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	11 (39.29)	17 (60.71)	NC (86.00, NC)	2.13	(0.78, 5.80)	0.109
	Placebo N=74	31	6 (19.35)	25 (80.65)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.13.1.7: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	13 (46.43)	15 (53.57)	NC (85.00, NC)	3.94	(1.11, 13.94)	0.042	0.187
	Placebo N=74	19	3 (15.79)	16 (84.21)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.7: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	23	4 (17.39)	19 (82.61)	NC (337.00, NC)	0.91	(0.23, 3.68)	0.988
	Placebo N=74	24	4 (16.67)	20 (83.33)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.7: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	2 (11.76)	15 (88.24)	NC (NC, NC)	0.72	(0.12, 4.45)	0.882
	Placebo N=74	29	4 (13.79)	25 (86.21)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.8: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	5 (25.00)	15 (75.00)	NC (167.00, NC)	4.35	(0.49, 38.64)	0.049	0.221
	Placebo N=74	21	1 (4.76)	20 (95.24)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.8: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	48	14 (29.17)	34 (70.83)	NC (NC, NC)	1.53	(0.68, 3.46)	0.294
	Placebo N=74	51	10 (19.61)	41 (80.39)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.9: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (NC, NC)	NC	(NC, NC)	0.296	0.611
	Placebo N=74	13	0 (0.00)	13 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.9: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	6	0 (0.00)	6 (100)	NC (NC, NC)	NC	(NC, NC)	NC
	Placebo N=74	8	0 (0.00)	8 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.9: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	9 (30.00)	21 (70.00)	NC (337.00, NC)	3.33	(0.90, 12.31)	0.053
	Placebo N=74	28	3 (10.71)	25 (89.29)	NC (NC, NC)			

CI = Confidence interval

Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.

Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.

[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.

The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.

PN = Plexiform neurofibroma

N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.

Full Analysis Set consists of subjects randomised to study intervention in the study.

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Table 8.13.1.9: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	21	9 (42.86)	12 (57.14)	NC (85.00, NC)	0.98	(0.36, 2.66)	0.594
	Placebo N=74	23	8 (34.78)	15 (65.22)	NC (114.00, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.1: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	11 (36.67)	19 (63.33)	NC (59.00, NC)	4.47	(1.54, 13.03)	0.026	0.116
	Placebo N=74	41	6 (14.63)	35 (85.37)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.1: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	8 (21.05)	30 (78.95)	NC (NC, NC)	1.40	(0.45, 4.40)	0.649
	Placebo N=74	31	5 (16.13)	26 (83.87)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.2: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	31	11 (35.48)	20 (64.52)	NC (281.00, NC)	2.74	(0.97, 7.72)	0.061	0.322
	Placebo N=74	40	6 (15.00)	34 (85.00)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.2: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	37	8 (21.62)	29 (78.38)	NC (NC, NC)	1.17	(0.38, 3.58)	0.495
	Placebo N=74	32	5 (15.63)	27 (84.38)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.13.1.3: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	2 (10.00)	18 (90.00)	NC (NC, NC)	NC	(NC, NC)	0.133	1.000
	Placebo N=74	23	0 (0.00)	23 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.13.1.3: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	12 (31.58)	26 (68.42)	NC (281.00, NC)	1.09	(0.47, 2.50)	0.625
	Placebo N=74	41	11 (26.83)	30 (73.17)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.13.1.3: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (141.00, NC)	NC	(NC, NC)	0.264
	Placebo N=74	5	0 (0.00)	5 (100)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.13.1.4: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	113.00 (57.00, NC)	0.79	(0.19, 3.24)	0.462	0.074
	Placebo N=74	9	6 (66.67)	3 (33.33)	29.00 (28.00, NC)				

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.13.1.4: Pain Medication - Time to first decrease in pain medication due to decreased PN pain using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	60	15 (25.00)	45 (75.00)	NC (NC, NC)	3.34	(1.21, 9.25)	0.010
	Placebo N=74	61	5 (8.20)	56 (91.80)	NC (NC, NC)			

CI = Confidence interval
Time to first decrease is time from randomisation to last day of the first cycle where first decrease in pain medication due to decreased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no decrease are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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1.1.7.6 Schmerz anhand der Schmerzmedikation – Zeit bis zum erstmaligen Anstieg der Schmerzmedikationl aufgrund von PN Schmerz basierend auf der Bewertung des Prüfarztes

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Table 8.10.1.1: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	5 (16.67)	25 (83.33)	NC (NC, NC)	1.11	(0.35, 3.55)	0.990	0.073
	Placebo N=74	41	7 (17.07)	34 (82.93)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.1: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	4 (10.53)	34 (89.47)	NC (343.00, NC)	0.25	(0.07, 0.84)	0.031
	Placebo N=74	31	9 (29.03)	22 (70.97)	NC (229.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.2: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	31	7 (22.58)	24 (77.42)	NC (NC, NC)	0.68	(0.25, 1.82)	0.493	0.491
	Placebo N=74	40	11 (27.50)	29 (72.50)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.2: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	37	2 (5.41)	35 (94.59)	NC (343.00, NC)	0.32	(0.06, 1.74)	0.155
	Placebo N=74	32	5 (15.63)	27 (84.38)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.3: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	1 (5.00)	19 (95.00)	NC (NC, NC)	0.09	(0.01, 1.46)	0.097	0.236
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.10.1.3: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	38	4 (10.53)	34 (89.47)	NC (343.00, NC)	0.37	(0.11, 1.19)	0.114
	Placebo N=74	41	10 (24.39)	31 (75.61)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.10.1.3: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (57.00, NC)	NC	(0.00, NC)	0.795
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (143.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 8.10.1.4: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (84.00, NC)	0.44	(0.05, 4.32)	0.336	0.765
	Placebo N=74	9	4 (44.44)	5 (55.56)	NC (56.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.10.1.4: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	60	7 (11.67)	53 (88.33)	NC (343.00, NC)	0.50	(0.19, 1.28)	0.213
	Placebo N=74	61	12 (19.67)	49 (80.33)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 8.10.1.5: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	9	1 (11.11)	8 (88.89)	NC (223.00, NC)	0.63	(0.04, 10.49)	0.755	0.925
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (58.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.5: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	26	3 (11.54)	23 (88.46)	NC (343.00, NC)	0.45	(0.11, 1.81)	0.252
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.5: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	1 (5.88)	16 (94.12)	NC (NC, NC)	0.28	(0.03, 2.95)	0.359
	Placebo N=74	21	3 (14.29)	18 (85.71)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.5: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	4 (25.00)	12 (75.00)	NC (169.00, NC)	0.70	(0.19, 2.66)	0.856
	Placebo N=74	20	6 (30.00)	14 (70.00)	NC (229.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.6: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	0 (0.00)	12 (100)	NC (NC, NC)	NC	(NC, NC)	0.085	0.953
	Placebo N=74	17	4 (23.53)	13 (76.47)	NC (229.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.10.1.6: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	12	1 (8.33)	11 (91.67)	NC (NC, NC)	NC	(0.00, NC)	1.000
	Placebo N=74	12	1 (8.33)	11 (91.67)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.10.1.6: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	16	3 (18.75)	13 (81.25)	NC (222.00, NC)	0.32	(0.02, 4.27)	0.969
	Placebo N=74	11	2 (18.18)	9 (81.82)	NC (225.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.10.1.6: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	5 (17.86)	23 (82.14)	NC (343.00, NC)	0.42	(0.14, 1.26)	0.213
	Placebo N=74	31	9 (29.03)	22 (70.97)	NC (313.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 8.10.1.7: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	28	6 (21.43)	22 (78.57)	NC (343.00, NC)	1.07	(0.30, 3.84)	0.896	0.260
	Placebo N=74	19	4 (21.05)	15 (78.95)	NC (303.00, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.7: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	23	1 (4.35)	22 (95.65)	NC (NC, NC)	0.16	(0.02, 1.47)	0.112
	Placebo N=74	24	5 (20.83)	19 (79.17)	NC (NC, NC)			

CI = Confidence interval

Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.

Subjects with no increase are censored at the day of last non-missing visit available during randomised period.

[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.

The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.

PN = Plexiform neurofibroma

N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.

Full Analysis Set consists of subjects randomised to study intervention in the study.

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Table 8.10.1.7: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Baseline Target PN Volume (Full Analysis Set)

Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	17	2 (11.76)	15 (88.24)	NC (NC, NC)	0.32	(0.06, 1.77)	0.314
	Placebo N=74	29	7 (24.14)	22 (75.86)	NC (NC, NC)			

CI = Confidence interval

Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.

Subjects with no increase are censored at the day of last non-missing visit available during randomised period.

[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.

The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.

PN = Plexiform neurofibroma

N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.

Full Analysis Set consists of subjects randomised to study intervention in the study.

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Table 8.10.1.8: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	20	1 (5.00)	19 (95.00)	343.00 (NC, NC)	0.00	(0.00, NC)	0.198	0.956
	Placebo N=74	21	2 (9.52)	19 (90.48)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.8: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	48	8 (16.67)	40 (83.33)	NC (NC, NC)	0.59	(0.24, 1.41)	0.156
	Placebo N=74	51	14 (27.45)	37 (72.55)	NC (NC, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.9: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	11	0 (0.00)	11 (100)	NC (NC, NC)	NC	(NC, NC)	NC	0.969
	Placebo N=74	13	0 (0.00)	13 (100)	NC (NC, NC)				

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 8.10.1.9: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (222.00, NC)	0.28	(0.03, 2.95)	0.396
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (29.00, NC)			

CI = Confidence interval

Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.

Subjects with no increase are censored at the day of last non-missing visit available during randomised period.

[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.

The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.

PN = Plexiform neurofibroma

N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.

Full Analysis Set consists of subjects randomised to study intervention in the study.

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Table 8.10.1.9: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)

Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	30	4 (13.33)	26 (86.67)	NC (343.00, NC)	0.61	(0.17, 2.15)	0.437
	Placebo N=74	28	6 (21.43)	22 (78.57)	NC (NC, NC)			

CI = Confidence interval

Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.

Subjects with no increase are censored at the day of last non-missing visit available during randomised period.

[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.

The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.

PN = Plexiform neurofibroma

N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.

Full Analysis Set consists of subjects randomised to study intervention in the study.

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Table 8.10.1.9: Pain Medication - Time to first increase in pain medication due to increased PN pain using the investigator assessment by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
Pain Medication Investigator Assessment	Selumetinib 25 mg/m2 BID N=71	21	4 (19.05)	17 (80.95)	NC (NC, NC)	0.47	(0.13, 1.68)	0.427
	Placebo N=74	23	7 (30.43)	16 (69.57)	NC (229.00, NC)			

CI = Confidence interval
Time to first increase is time from randomisation to last day of the first cycle where first increase in pain medication due to increased PN pain compared with the baseline medication is achieved as per the investigator assessment.
Subjects with no increase are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects with non-missing pain medication score at baseline and investigator pain medication assessment available for at least one post-baseline visit.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.8 Endpunkt Tägliche Funktionsfähigkeit anhand PII-pNF

1.1.8.1 Tägliche Funktionsfähigkeit anhand PII-pNF – Zeit bis zur erstmaligen Verbesserung ≥ 0,9 Punkte

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Table 15.2.1.9: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	11	8 (72.73)	3 (27.27)	29.00 (26.00, NC)	2.75	(0.86, 8.80)	0.097	0.150
	Placebo N=74	13	5 (38.46)	8 (61.54)	NC (28.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.9: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	6	2 (33.33)	4 (66.67)	NC (29.00, NC)	0.40	(0.07, 2.42)	0.491
	Placebo N=74	8	4 (50.00)	4 (50.00)	NC (29.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.9: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	30	21 (70.00)	9 (30.00)	57.00 (31.00, 225.00)	0.78	(0.43, 1.41)	0.370
	Placebo N=74	29	23 (79.31)	6 (20.69)	56.00 (29.00, 113.00)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.9: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	20	12 (60.00)	8 (40.00)	169.00 (57.00, NC)	1.19	(0.51, 2.78)	0.521
	Placebo N=74	22	11 (50.00)	11 (50.00)	225.00 (57.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.1: PII-pNF - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	30	20 (66.67)	10 (33.33)	60.00 (30.00, 225.00)	1.35	(0.72, 2.56)	0.462	0.450
	Placebo N=74	40	23 (57.50)	17 (42.50)	114.00 (29.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.1: PII-pNF - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	37	23 (62.16)	14 (37.84)	113.00 (57.00, NC)	0.93	(0.50, 1.72)	0.855
	Placebo N=74	32	20 (62.50)	12 (37.50)	113.00 (56.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.2: PII-pNF - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	30	22 (73.33)	8 (26.67)	57.50 (30.00, 225.00)	1.00	(0.56, 1.78)	0.803	0.821
	Placebo N=74	42	28 (66.67)	14 (33.33)	57.00 (29.00, 223.00)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.2: PII-pNF - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	37	21 (56.76)	16 (43.24)	114.00 (56.00, NC)	0.95	(0.46, 1.95)	0.555
	Placebo N=74	30	15 (50.00)	15 (50.00)	225.00 (106.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.3: PII-pNF - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	19	11 (57.89)	8 (42.11)	113.00 (28.00, NC)	1.71	(0.69, 4.23)	0.485	0.248
	Placebo N=74	23	11 (47.83)	12 (52.17)	NC (29.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 15.2.1.3: PII-pNF - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	38	23 (60.53)	15 (39.47)	111.00 (56.00, NC)	0.72	(0.42, 1.26)	0.361
	Placebo N=74	41	29 (70.73)	12 (29.27)	61.00 (30.00, 167.00)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 15.2.1.3: PII-pNF - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	4	4 (100)	0 (0.00)	85.50 (30.00, NC)	2.24	(0.23, 22.07)	0.474
	Placebo N=74	5	3 (60.00)	2 (40.00)	223.00 (29.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 15.2.1.4: PII-pNF - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	224.00 (28.00, NC)	0.41	(0.08, 2.23)	0.320	0.366
	Placebo N=74	8	7 (87.50)	1 (12.50)	43.00 (28.00, 225.00)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 15.2.1.4: PII-pNF - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	59	37 (62.71)	22 (37.29)	111.00 (56.00, 225.00)	1.14	(0.71, 1.83)	0.459
	Placebo N=74	62	34 (54.84)	28 (45.16)	167.00 (57.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 15.2.1.5: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	8	5 (62.50)	3 (37.50)	197.00 (25.00, NC)	3.28	(0.59, 18.26)	0.295	0.228
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (114.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.5: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	26	18 (69.23)	8 (30.77)	58.00 (42.00, 333.00)	0.87	(0.46, 1.66)	0.520
	Placebo N=74	26	20 (76.92)	6 (23.08)	58.50 (29.00, 167.00)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.5: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	17	10 (58.82)	7 (41.18)	113.00 (28.00, NC)	1.81	(0.71, 4.60)	0.321
	Placebo N=74	21	9 (42.86)	12 (57.14)	NC (29.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.5: PII-pNF - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	16	10 (62.50)	6 (37.50)	58.00 (30.00, NC)	0.52	(0.19, 1.38)	0.826
	Placebo N=74	19	12 (63.16)	7 (36.84)	112.00 (29.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.6: PII-pNF - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	6 (50.00)	225.00 (28.00, NC)	0.30	(0.10, 0.87)	0.142	0.023
	Placebo N=74	18	14 (77.78)	4 (22.22)	56.50 (29.00, 167.00)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.2.1.6: PII-pNF - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	6 (50.00)	NC (29.00, NC)	0.98	(0.25, 3.83)	0.343
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (32.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.2.1.6: PII-pNF - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	15	11 (73.33)	4 (26.67)	31.00 (27.00, 106.00)	9.54	(1.94, 46.91)	0.137
	Placebo N=74	11	5 (45.45)	6 (54.55)	223.00 (28.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.2.1.6: PII-pNF - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	28	20 (71.43)	8 (28.57)	111.00 (56.00, 225.00)	0.96	(0.50, 1.83)	0.790
	Placebo N=74	30	20 (66.67)	10 (33.33)	60.00 (29.00, 168.00)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.2.1.7: PII-pNF - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	28	21 (75.00)	7 (25.00)	58.00 (56.00, 224.00)	1.02	(0.49, 2.13)	0.996	0.691
	Placebo N=74	18	12 (66.67)	6 (33.33)	61.00 (29.00, 167.00)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.7: PII-pNF - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	23	15 (65.22)	8 (34.78)	57.00 (29.00, NC)	1.17	(0.57, 2.40)	0.605
	Placebo N=74	25	15 (60.00)	10 (40.00)	106.00 (29.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.7: PII-pNF - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	16	7 (43.75)	9 (56.25)	NC (30.00, NC)	0.64	(0.26, 1.60)	0.393
	Placebo N=74	29	16 (55.17)	13 (44.83)	225.00 (56.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.8: PII-pNF - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	20	7 (35.00)	13 (65.00)	NC (58.00, NC)	1.74	(0.50, 6.06)	0.320	0.256
	Placebo N=74	20	4 (20.00)	16 (80.00)	NC (NC, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.2.1.8: PII-pNF - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	47	36 (76.60)	11 (23.40)	57.00 (31.00, 113.00)	0.94	(0.59, 1.50)	0.909
	Placebo N=74	52	39 (75.00)	13 (25.00)	57.00 (29.00, 113.00)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.8.2 Tägliche Funktionsfähigkeit anhand PII-pNF – Zeit bis zur erstmaligen Verschlechterung ≥ 0,9 Punkte

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Table 15.5.1.5: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	8	1 (12.50)	7 (87.50)	NC (223.00, NC)	0.50	(0.03, 9.52)	0.825	0.832
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (121.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.5: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	26	5 (19.23)	21 (80.77)	NC (NC, NC)	0.91	(0.28, 3.02)	0.879
	Placebo N=74	26	6 (23.08)	20 (76.92)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.5: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	17	4 (23.53)	13 (76.47)	NC (225.00, NC)	0.91	(0.24, 3.46)	0.963
	Placebo N=74	21	5 (23.81)	16 (76.19)	NC (335.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.5: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	16	1 (6.25)	15 (93.75)	NC (NC, NC)	0.32	(0.04, 2.88)	0.257
	Placebo N=74	19	4 (21.05)	15 (78.95)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.6: PII-pNF - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	12	1 (8.33)	11 (91.67)	NC (NC, NC)	0.52	(0.05, 5.55)	0.329	0.707
	Placebo N=74	18	4 (22.22)	14 (77.78)	NC (287.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.5.1.6: PII-pNF - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	12	2 (16.67)	10 (83.33)	NC (223.00, NC)	1.66	(0.14, 20.00)	0.547
	Placebo N=74	12	1 (8.33)	11 (91.67)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.5.1.6: PII-pNF - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	15	4 (26.67)	11 (73.33)	NC (30.00, NC)	0.75	(0.16, 3.50)	0.485
	Placebo N=74	11	5 (45.45)	6 (54.55)	NC (57.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.5.1.6: PII-pNF - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	28	4 (14.29)	24 (85.71)	NC (NC, NC)	0.62	(0.17, 2.28)	0.569
	Placebo N=74	30	6 (20.00)	24 (80.00)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 15.5.1.7: PII-pNF - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	28	5 (17.86)	23 (82.14)	NC (NC, NC)	0.96	(0.22, 4.15)	0.990	0.527
	Placebo N=74	18	3 (16.67)	15 (83.33)	NC (335.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.7: PII-pNF - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	23	2 (8.70)	21 (91.30)	NC (NC, NC)	0.36	(0.07, 1.79)	0.215
	Placebo N=74	25	6 (24.00)	19 (76.00)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.7: PII-pNF - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	16	4 (25.00)	12 (75.00)	NC (225.00, NC)	1.33	(0.37, 4.81)	0.794
	Placebo N=74	29	7 (24.14)	22 (75.86)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.8: PII-pNF - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	20	2 (10.00)	18 (90.00)	NC (NC, NC)	0.18	(0.02, 1.57)	0.178	0.291
	Placebo N=74	20	6 (30.00)	14 (70.00)	NC (223.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.8: PII-pNF - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	47	9 (19.15)	38 (80.85)	NC (NC, NC)	1.10	(0.44, 2.75)	0.999
	Placebo N=74	52	10 (19.23)	42 (80.77)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.9: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (NC, NC)	0.29	(0.03, 2.68)	0.202	0.221
	Placebo N=74	13	4 (30.77)	9 (69.23)	NC (58.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.9: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	6	3 (50.00)	3 (50.00)	NC (29.00, NC)	5.86	(0.59, 58.63)	0.089
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (335.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.9: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	30	5 (16.67)	25 (83.33)	NC (NC, NC)	0.89	(0.27, 2.93)	0.858
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.9: PII-pNF - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	20	2 (10.00)	18 (90.00)	NC (NC, NC)	0.40	(0.08, 2.08)	0.280
	Placebo N=74	22	5 (22.73)	17 (77.27)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.1: PII-pNF - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	30	4 (13.33)	26 (86.67)	NC (NC, NC)	0.60	(0.18, 2.00)	0.391	0.752
	Placebo N=74	40	9 (22.50)	31 (77.50)	NC (NC, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.1: PII-pNF - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	37	7 (18.92)	30 (81.08)	NC (NC, NC)	0.75	(0.26, 2.22)	0.788
	Placebo N=74	32	7 (21.88)	25 (78.13)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.2: PII-pNF - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	30	5 (16.67)	25 (83.33)	NC (NC, NC)	0.64	(0.21, 1.89)	0.419	0.573
	Placebo N=74	42	10 (23.81)	32 (76.19)	NC (NC, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.2: PII-pNF - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	37	6 (16.22)	31 (83.78)	NC (NC, NC)	0.87	(0.27, 2.80)	0.876
	Placebo N=74	30	6 (20.00)	24 (80.00)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 15.5.1.3: PII-pNF - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	19	4 (21.05)	15 (78.95)	NC (NC, NC)	0.91	(0.24, 3.46)	0.938	0.947
	Placebo N=74	23	5 (21.74)	18 (78.26)	NC (335.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 15.5.1.3: PII-pNF - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	38	5 (13.16)	33 (86.84)	NC (NC, NC)	0.73	(0.24, 2.24)	0.552
	Placebo N=74	41	8 (19.51)	33 (80.49)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 15.5.1.3: PII-pNF - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	4	0 (0.00)	4 (100)	NC (NC, NC)	NC	(NC, NC)	0.180
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (162.00, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 15.5.1.4: PII-pNF - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (28.00, NC)	0.71	(0.03, 16.98)	0.888	0.785
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (57.00, NC)				

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 15.5.1.4: PII-pNF - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PII-pNF	Selumetinib 25 mg/m2 BID N=71	59	10 (16.95)	49 (83.05)	NC (NC, NC)	0.87	(0.38, 1.99)	0.660
	Placebo N=74	62	13 (20.97)	49 (79.03)	NC (NC, NC)			

PII-pNF = Pain Interference Index for Plexiform Neurofibroma; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 0.9 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proprtional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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1.1.9 Endpunkt Gesundheitszustand anhand EQ-5D VAS

1.1.9.1 Gesundheitszustand anhand EQ-5D VAS – Zeit bis zur erstmaligen Verbesserung um ≥ 15 Punkte

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Table 13.2.1.4: EQ-VAS - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (109.00, NC)	0.24	(0.01, 7.15)	0.459	0.288
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (57.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 13.2.1.4: EQ-VAS - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	56	23 (41.07)	33 (58.93)	340.00 (225.00, NC)	1.27	(0.70, 2.32)	0.591
	Placebo N=74	61	21 (34.43)	40 (65.57)	NC (341.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 13.2.1.5: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	8	2 (25.00)	6 (75.00)	NC (63.00, NC)	NC	(NC, NC)	0.165	0.343
	Placebo N=74	6	0 (0.00)	6 (100)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.5: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	25	10 (40.00)	15 (60.00)	340.00 (114.00, NC)	0.75	(0.32, 1.72)	0.381
	Placebo N=74	26	13 (50.00)	13 (50.00)	341.00 (62.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.5: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	17	10 (58.82)	7 (41.18)	225.00 (57.00, NC)	4.05	(1.20, 13.69)	0.119
	Placebo N=74	20	6 (30.00)	14 (70.00)	NC (58.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.5: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	14	5 (35.71)	9 (64.29)	NC (58.00, NC)	0.82	(0.24, 2.82)	0.926
	Placebo N=74	19	6 (31.58)	13 (68.42)	NC (57.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.6: EQ-VAS - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	11	4 (36.36)	7 (63.64)	340.00 (57.00, NC)	0.40	(0.12, 1.35)	0.153	0.122
	Placebo N=74	18	10 (55.56)	8 (44.44)	113.00 (56.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.2.1.6: EQ-VAS - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	6 (50.00)	114.00 (60.00, NC)	1.07	(0.22, 5.27)	0.220
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (62.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.2.1.6: EQ-VAS - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	14	5 (35.71)	9 (64.29)	NC (58.00, NC)	31.3	(1.02, 956.8)	0.152
	Placebo N=74	11	2 (18.18)	9 (81.82)	341.00 (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.2.1.6: EQ-VAS - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	27	12 (44.44)	15 (55.56)	NC (109.00, NC)	1.55	(0.66, 3.65)	0.506
	Placebo N=74	29	10 (34.48)	19 (65.52)	NC (115.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.2.1.7: EQ-VAS - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	28	14 (50.00)	14 (50.00)	225.00 (114.00, NC)	0.67	(0.26, 1.72)	0.820	0.061
	Placebo N=74	17	8 (47.06)	9 (52.94)	NC (57.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.7: EQ-VAS - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	21	10 (47.62)	11 (52.38)	340.00 (57.00, NC)	2.75	(0.98, 7.75)	0.123
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (330.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.7: EQ-VAS - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	15	3 (20.00)	12 (80.00)	NC (109.00, NC)	0.50	(0.13, 1.89)	0.317
	Placebo N=74	29	10 (34.48)	19 (65.52)	NC (58.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.8: EQ-VAS - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	18	3 (16.67)	15 (83.33)	NC (NC, NC)	1.04	(0.21, 5.22)	0.848	0.929
	Placebo N=74	20	3 (15.00)	17 (85.00)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.8: EQ-VAS - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	46	24 (52.17)	22 (47.83)	336.00 (112.00, NC)	1.23	(0.68, 2.22)	0.562
	Placebo N=74	51	22 (43.14)	29 (56.86)	341.00 (113.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.9: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	11	8 (72.73)	3 (27.27)	225.00 (55.00, NC)	4.33	(1.01, 18.62)	0.118	0.356
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (57.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.9: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	6	2 (33.33)	4 (66.67)	NC (57.00, NC)	2.20	(0.25, 19.55)	0.742
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (57.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.9: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	28	12 (42.86)	16 (57.14)	340.00 (114.00, NC)	0.89	(0.41, 1.93)	0.613
	Placebo N=74	29	14 (48.28)	15 (51.72)	341.00 (62.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.9: EQ-VAS - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	19	5 (26.32)	14 (73.68)	NC (113.00, NC)	1.06	(0.30, 3.71)	0.824
	Placebo N=74	22	5 (22.73)	17 (77.27)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.1: EQ-VAS - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	28	16 (57.14)	12 (42.86)	225.00 (113.00, NC)	2.12	(0.98, 4.58)	0.063	0.055
	Placebo N=74	39	12 (30.77)	27 (69.23)	NC (341.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.1: EQ-VAS - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	36	11 (30.56)	25 (69.44)	NC (340.00, NC)	0.75	(0.33, 1.71)	0.323
	Placebo N=74	32	13 (40.63)	19 (59.38)	NC (113.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.2: EQ-VAS - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	30	13 (43.33)	17 (56.67)	340.00 (225.00, NC)	1.47	(0.67, 3.26)	0.449	0.637
	Placebo N=74	41	13 (31.71)	28 (68.29)	NC (341.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.2: EQ-VAS - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	34	14 (41.18)	20 (58.82)	NC (114.00, NC)	1.17	(0.49, 2.81)	0.983
	Placebo N=74	30	12 (40.00)	18 (60.00)	NC (62.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.2.1.3: EQ-VAS - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	19	10 (52.63)	9 (47.37)	336.00 (57.00, NC)	4.05	(1.20, 13.69)	0.134	0.153
	Placebo N=74	22	6 (27.27)	16 (72.73)	NC (230.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 13.2.1.3: EQ-VAS - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	35	14 (40.00)	21 (60.00)	340.00 (114.00, NC)	0.87	(0.43, 1.77)	0.761
	Placebo N=74	41	17 (41.46)	24 (58.54)	NC (113.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 13.2.1.3: EQ-VAS - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	4	3 (75.00)	1 (25.00)	113.50 (57.00, NC)	14.3	(0.67, 307.0)	0.210
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (113.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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1.1.9.2 Gesundheitszustand anhand EQ-5D VAS – Zeit bis zur erstmaligen Verschlechterung um ≥ 15 Punkte

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Table 13.5.1.3: EQ-VAS - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	19	6 (31.58)	13 (68.42)	NC (225.00, NC)	1.62	(0.48, 5.52)	0.578	0.838
	Placebo N=74	22	5 (22.73)	17 (77.27)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 13.5.1.3: EQ-VAS - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	35	11 (31.43)	24 (68.57)	339.00 (338.00, NC)	1.75	(0.70, 4.39)	0.205
	Placebo N=74	41	8 (19.51)	33 (80.49)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 13.5.1.3: EQ-VAS - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (57.00, NC)	0.00	(0.00, NC)	0.795
	Placebo N=74	5	1 (20.00)	4 (80.00)	NC (113.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 13.5.1.4: EQ-VAS - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (57.00, NC)	1.84	(0.15, 22.19)	0.871	0.330
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (57.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 13.5.1.4: EQ-VAS - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	56	22 (39.29)	34 (60.71)	339.00 (253.00, NC)	2.35	(1.16, 4.80)	0.024
	Placebo N=74	61	12 (19.67)	49 (80.33)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 13.5.1.5: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	8	2 (25.00)	6 (75.00)	NC (223.00, NC)	0.85	(0.05, 13.61)	0.610	0.848
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (58.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.5: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	25	10 (40.00)	15 (60.00)	338.00 (121.00, NC)	1.57	(0.60, 4.13)	0.362
	Placebo N=74	26	7 (26.92)	19 (73.08)	NC (224.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.5: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (113.00, NC)	1.62	(0.48, 5.52)	0.556
	Placebo N=74	20	5 (25.00)	15 (75.00)	NC (114.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.5: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	14	5 (35.71)	9 (64.29)	339.00 (106.00, NC)	3.49	(0.67, 18.22)	0.094
	Placebo N=74	19	2 (10.53)	17 (89.47)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.6: EQ-VAS - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	11	4 (36.36)	7 (63.64)	339.00 (112.00, NC)	3.92	(0.59, 26.21)	0.234	0.820
	Placebo N=74	18	3 (16.67)	15 (83.33)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.5.1.6: EQ-VAS - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (121.00, NC)	2.51	(0.23, 27.46)	0.262
	Placebo N=74	12	1 (8.33)	11 (91.67)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.5.1.6: EQ-VAS - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	14	8 (57.14)	6 (42.86)	169.50 (58.00, NC)	0.82	(0.21, 3.26)	0.570
	Placebo N=74	11	5 (45.45)	6 (54.55)	NC (58.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.5.1.6: EQ-VAS - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	27	8 (29.63)	19 (70.37)	NC (338.00, NC)	1.35	(0.46, 3.94)	0.572
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 13.5.1.7: EQ-VAS - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	28	7 (25.00)	21 (75.00)	NC (NC, NC)	5.25	(0.64, 43.00)	0.108	0.256
	Placebo N=74	17	1 (5.88)	16 (94.12)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.7: EQ-VAS - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	21	8 (38.10)	13 (61.90)	339.00 (246.00, NC)	1.09	(0.41, 2.93)	0.775
	Placebo N=74	25	8 (32.00)	17 (68.00)	NC (112.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.7: EQ-VAS - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	15	8 (53.33)	7 (46.67)	253.00 (57.00, NC)	2.93	(1.00, 8.58)	0.034
	Placebo N=74	29	6 (20.69)	23 (79.31)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.8: EQ-VAS - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	18	7 (38.89)	11 (61.11)	NC (110.00, NC)	4.22	(1.03, 17.24)	0.068	0.298
	Placebo N=74	20	3 (15.00)	17 (85.00)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.8: EQ-VAS - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	46	16 (34.78)	30 (65.22)	NC (338.00, NC)	1.53	(0.72, 3.26)	0.319
	Placebo N=74	51	12 (23.53)	39 (76.47)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.9: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	11	2 (18.18)	9 (81.82)	NC (225.00, NC)	0.51	(0.09, 2.94)	0.381	0.230
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (57.00, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.9: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	2 (33.33)	169.00 (53.00, NC)	6.85	(0.75, 62.21)	0.051
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (56.00, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.9: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	28	11 (39.29)	17 (60.71)	NC (121.00, NC)	1.77	(0.69, 4.58)	0.230
	Placebo N=74	29	7 (24.14)	22 (75.86)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.9: EQ-VAS - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	19	6 (31.58)	13 (68.42)	339.00 (246.00, NC)	2.30	(0.56, 9.46)	0.170
	Placebo N=74	22	3 (13.64)	19 (86.36)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.1: EQ-VAS - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	28	6 (21.43)	22 (78.57)	NC (NC, NC)	0.96	(0.34, 2.76)	0.795	0.117
	Placebo N=74	39	9 (23.08)	30 (76.92)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.1: EQ-VAS - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	36	17 (47.22)	19 (52.78)	339.00 (225.00, NC)	2.88	(1.13, 7.39)	0.022
	Placebo N=74	32	6 (18.75)	26 (81.25)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.2: EQ-VAS - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	30	11 (36.67)	19 (63.33)	NC (246.00, NC)	1.69	(0.69, 4.19)	0.206	0.837
	Placebo N=74	41	9 (21.95)	32 (78.05)	NC (NC, NC)				

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 13.5.1.2: EQ-VAS - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
EQ-VAS	Selumetinib 25 mg/m2 BID N=71	34	12 (35.29)	22 (64.71)	NC (226.00, NC)	1.65	(0.60, 4.56)	0.169
	Placebo N=74	30	6 (20.00)	24 (80.00)	NC (NC, NC)			

EQ-VAS = EuroQoL-visual analogue scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.10 Endpunkt Körperliche Funktionsfähigkeit anhand PROMIS

1.1.10.1 Körperliche Funktionsfähigkeit anhand PROMIS – Zeit bis zur erstmaligen Verbesserung um ≥ 5,85 Punkte

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Table 16.2.1.1: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	28	11 (39.29)	17 (60.71)	NC (120.00, NC)	0.76	(0.35, 1.65)	0.705	0.671
	Placebo N=74	39	16 (41.03)	23 (58.97)	NC (112.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.1: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	36	15 (41.67)	21 (58.33)	NC (117.00, NC)	1.04	(0.49, 2.20)	0.948
	Placebo N=74	32	13 (40.63)	19 (59.38)	343.00 (113.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.2: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	30	16 (53.33)	14 (46.67)	226.00 (113.00, NC)	1.49	(0.73, 3.04)	0.509	0.047
	Placebo N=74	41	16 (39.02)	25 (60.98)	340.00 (113.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.2: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	34	10 (29.41)	24 (70.59)	NC (225.00, NC)	0.47	(0.20, 1.11)	0.251
	Placebo N=74	30	13 (43.33)	17 (56.67)	343.00 (112.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.3: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	19	5 (26.32)	14 (73.68)	NC (227.00, NC)	0.72	(0.21, 2.46)	0.607	0.914
	Placebo N=74	22	7 (31.82)	15 (68.18)	338.00 (112.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 16.2.1.3: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	35	16 (45.71)	19 (54.29)	NC (113.00, NC)	0.88	(0.45, 1.70)	0.760
	Placebo N=74	41	20 (48.78)	21 (51.22)	340.00 (112.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 16.2.1.3: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	2 (50.00)	NC (107.00, NC)	0.00	(0.00, NC)	0.967
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (57.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 16.2.1.4: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	224.00 (57.00, NC)	2.53	(0.34, 18.95)	0.311	0.455
	Placebo N=74	8	3 (37.50)	5 (62.50)	340.00 (112.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 16.2.1.4: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	56	22 (39.29)	34 (60.71)	NC (225.00, NC)	0.92	(0.51, 1.64)	0.780
	Placebo N=74	61	24 (39.34)	37 (60.66)	343.00 (226.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 16.2.1.5: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	8	3 (37.50)	5 (62.50)	NC (111.00, NC)	3.08	(0.31, 30.86)	0.265	0.433
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (338.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.5: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	25	11 (44.00)	14 (56.00)	NC (113.00, NC)	0.62	(0.28, 1.35)	0.230
	Placebo N=74	26	15 (57.69)	11 (42.31)	113.00 (58.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.5: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	17	4 (23.53)	13 (76.47)	NC (227.00, NC)	0.73	(0.19, 2.76)	0.746
	Placebo N=74	20	5 (25.00)	15 (75.00)	NC (58.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.5: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	14	8 (57.14)	6 (42.86)	169.00 (58.00, NC)	1.71	(0.58, 4.99)	0.282
	Placebo N=74	19	8 (42.11)	11 (57.89)	340.00 (113.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.6: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	11	4 (36.36)	7 (63.64)	NC (57.00, NC)	0.57	(0.17, 1.93)	0.478	0.627
	Placebo N=74	18	9 (50.00)	9 (50.00)	343.00 (58.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 16.2.1.6: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	6 (50.00)	NC (60.00, NC)	1.71	(0.41, 7.11)	0.251
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (57.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 16.2.1.6: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	14	3 (21.43)	11 (78.57)	NC (113.00, NC)	1.20	(0.17, 8.49)	0.635
	Placebo N=74	11	3 (27.27)	8 (72.73)	NC (57.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 16.2.1.6: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	27	13 (48.15)	14 (51.85)	NC (114.00, NC)	0.85	(0.39, 1.81)	0.742
	Placebo N=74	29	14 (48.28)	15 (51.72)	338.00 (112.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 16.2.1.7: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	28	14 (50.00)	14 (50.00)	225.00 (113.00, NC)	0.93	(0.38, 2.30)	0.985	0.734
	Placebo N=74	17	8 (47.06)	9 (52.94)	338.00 (57.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.7: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	21	9 (42.86)	12 (57.14)	NC (111.00, NC)	0.83	(0.35, 1.98)	0.729
	Placebo N=74	25	12 (48.00)	13 (52.00)	340.00 (112.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.7: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	15	3 (20.00)	12 (80.00)	NC (227.00, NC)	0.46	(0.12, 1.75)	0.325
	Placebo N=74	29	9 (31.03)	20 (68.97)	NC (112.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.8: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	18	6 (33.33)	12 (66.67)	NC (117.00, NC)	0.61	(0.21, 1.76)	0.443	0.496
	Placebo N=74	20	9 (45.00)	11 (55.00)	NC (57.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.8: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	46	20 (43.48)	26 (56.52)	NC (120.00, NC)	0.98	(0.53, 1.83)	0.938
	Placebo N=74	51	20 (39.22)	31 (60.78)	343.00 (217.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.9: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	NC (224.00, NC)	0.82	(0.16, 4.13)	0.911	0.597
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (56.00, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.9: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (106.00, NC)	0.57	(0.05, 6.34)	0.651
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (56.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.9: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	28	13 (46.43)	15 (53.57)	NC (113.00, NC)	0.66	(0.32, 1.35)	0.265
	Placebo N=74	29	17 (58.62)	12 (41.38)	113.00 (58.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 16.2.1.9: PROMIS, T-score - Time to first improvement by >=15% scale range for transformed total score by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	19	9 (47.37)	10 (52.63)	NC (113.00, NC)	1.57	(0.58, 4.25)	0.317
	Placebo N=74	22	7 (31.82)	15 (68.18)	340.00 (338.00, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.1.10.2 Körperliche Funktionsfähigkeit anhand PROMIS – Zeit bis zur erstmaligen Verschlechterung um ≥ 5,85 Punkte

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Table 16.5.1.4: PROMIS, T-score - Time to first deterioration by >=15% scale range for transformed total score by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PROMIS	Selumetinib 25 mg/m2 BID N=71	5	0 (0.00)	5 (100)	NC (NC, NC)	NC	(NC, NC)	NC	1.000
	Placebo N=74	8	0 (0.00)	8 (100)	NC (NC, NC)				

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 16.5.1.4: PROMIS, T-score - Time to first deterioration by >=15% scale range for transformed total score by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PROMIS	Selumetinib 25 mg/m2 BID N=71	56	7 (12.50)	49 (87.50)	NC (NC, NC)	1.29	(0.43, 3.88)	0.644
	Placebo N=74	61	6 (9.84)	55 (90.16)	NC (NC, NC)			

PROMIS = Patient-Reported Outcomes Measurement Information System; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 5.85 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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1.2 Endpunktkategorie Gesundheitsbezogene Lebensqualität

1.2.1 Endpunkt Gesundheitsbezogene Lebensqualität anhand PlexiQoL

1.2.1.1 Gesundheitsbezogene Lebensqualität anhand PlexiQoL – Zeit bis zur erstmaligen Verbesserung des chronischen Schmerzes um ≥ 2,7 Punkte

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Table 20.2.1.1: PlexiQoL - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	28	11 (39.29)	17 (60.71)	342.00 (120.00, NC)	0.62	(0.29, 1.32)	0.212	0.442
	Placebo N=74	39	20 (51.28)	19 (48.72)	338.00 (112.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.1: PlexiQoL - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	36	18 (50.00)	18 (50.00)	337.00 (113.00, NC)	1.00	(0.49, 2.02)	0.971
	Placebo N=74	32	14 (43.75)	18 (56.25)	336.00 (61.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.2: PlexiQoL - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	30	19 (63.33)	11 (36.67)	278.00 (112.00, NC)	1.41	(0.73, 2.71)	0.336	0.023
	Placebo N=74	41	18 (43.90)	23 (56.10)	351.00 (224.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.2: PlexiQoL - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	34	10 (29.41)	24 (70.59)	NC (328.00, NC)	0.41	(0.17, 0.97)	0.056
	Placebo N=74	30	16 (53.33)	14 (46.67)	336.00 (58.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.3: PlexiQoL - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	19	9 (47.37)	10 (52.63)	337.00 (57.00, NC)	0.93	(0.36, 2.42)	0.490	0.869
	Placebo N=74	22	12 (54.55)	10 (45.45)	336.00 (58.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 20.2.1.3: PlexiQoL - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	35	17 (48.57)	18 (51.43)	342.00 (113.00, NC)	0.87	(0.45, 1.69)	0.800
	Placebo N=74	41	20 (48.78)	21 (51.22)	333.00 (61.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 20.2.1.3: PlexiQoL - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	4	1 (25.00)	3 (75.00)	NC (226.00, NC)	1.52	(0.05, 48.21)	0.743
	Placebo N=74	5	2 (40.00)	3 (60.00)	336.00 (225.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 20.2.1.4: PlexiQoL - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	3 (60.00)	NC (57.00, NC)	0.00	(0.00, NC)	0.522	0.747
	Placebo N=74	8	4 (50.00)	4 (50.00)	336.00 (56.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 20.2.1.4: PlexiQoL - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	56	26 (46.43)	30 (53.57)	342.00 (121.00, NC)	0.89	(0.52, 1.52)	0.670
	Placebo N=74	61	29 (47.54)	32 (52.46)	336.00 (113.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 20.2.1.5: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	8	6 (75.00)	2 (25.00)	84.50 (51.00, NC)	7.62	(1.17, 49.50)	0.082	0.113
	Placebo N=74	6	2 (33.33)	4 (66.67)	NC (57.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.5: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	25	8 (32.00)	17 (68.00)	NC (328.00, NC)	0.40	(0.17, 0.96)	0.028
	Placebo N=74	26	15 (57.69)	11 (42.31)	232.00 (61.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.5: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	17	8 (47.06)	9 (52.94)	337.00 (57.00, NC)	0.93	(0.33, 2.62)	0.531
	Placebo N=74	20	10 (50.00)	10 (50.00)	336.00 (57.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.5: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	14	7 (50.00)	7 (50.00)	NC (57.00, NC)	0.33	(0.09, 1.30)	0.785
	Placebo N=74	19	7 (36.84)	12 (63.16)	NC (110.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.6: PlexiQoL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	4 (36.36)	112.00 (57.00, NC)	1.34	(0.44, 4.06)	0.433	0.493
	Placebo N=74	18	8 (44.44)	10 (55.56)	NC (110.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.2.1.6: PlexiQoL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	12	4 (33.33)	8 (66.67)	NC (113.00, NC)	1.09	(0.22, 5.31)	0.622
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (58.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.2.1.6: PlexiQoL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	14	6 (42.86)	8 (57.14)	NC (57.00, NC)	1.87	(0.30, 11.72)	0.901
	Placebo N=74	11	4 (36.36)	7 (63.64)	NC (57.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.2.1.6: PlexiQoL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	27	12 (44.44)	15 (55.56)	342.00 (115.00, NC)	0.52	(0.24, 1.10)	0.062
	Placebo N=74	29	19 (65.52)	10 (34.48)	232.00 (58.00, 338.00)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.2.1.7: PlexiQoL - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	28	11 (39.29)	17 (60.71)	342.00 (113.00, NC)	0.57	(0.24, 1.36)	0.156	0.132
	Placebo N=74	17	11 (64.71)	6 (35.29)	224.00 (57.00, 351.00)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.7: PlexiQoL - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	21	13 (61.90)	8 (38.10)	226.00 (57.00, NC)	1.52	(0.65, 3.53)	0.182
	Placebo N=74	25	10 (40.00)	15 (60.00)	336.00 (225.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.7: PlexiQoL - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	15	5 (33.33)	10 (66.67)	NC (115.00, NC)	0.53	(0.18, 1.55)	0.297
	Placebo N=74	29	13 (44.83)	16 (55.17)	NC (58.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.8: PlexiQoL - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	18	6 (33.33)	12 (66.67)	342.00 (330.00, NC)	1.09	(0.30, 4.00)	0.919	0.594
	Placebo N=74	20	5 (25.00)	15 (75.00)	NC (112.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.8: PlexiQoL - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	46	23 (50.00)	23 (50.00)	331.00 (113.00, NC)	0.78	(0.45, 1.37)	0.324
	Placebo N=74	51	29 (56.86)	22 (43.14)	232.00 (111.00, 338.00)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.9: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	11	4 (36.36)	7 (63.64)	NC (58.00, NC)	0.53	(0.15, 1.93)	0.240	0.038
	Placebo N=74	12	7 (58.33)	5 (41.67)	280.00 (57.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.9: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	2 (33.33)	197.00 (53.00, NC)	1.75	(0.34, 8.94)	0.633
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (56.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.9: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	28	10 (35.71)	18 (64.29)	342.00 (226.00, NC)	0.42	(0.19, 0.92)	0.020
	Placebo N=74	29	18 (62.07)	11 (37.93)	225.00 (58.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.2.1.9: PlexiQoL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	19	11 (57.89)	8 (42.11)	120.00 (57.00, NC)	2.12	(0.77, 5.85)	0.072
	Placebo N=74	22	6 (27.27)	16 (72.73)	NC (336.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score. Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.2.1.2 Gesundheitsbezogene Lebensqualität anhand PlexiQoL – Zeit bis zur erstmaligen Verschlechterung des chronischen Schmerzes um ≥ 2,7 Punkte

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Table 20.5.1.1: PlexiQoL - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	28	10 (35.71)	18 (64.29)	339.00 (337.00, NC)	1.25	(0.51, 3.07)	0.356	0.208
	Placebo N=74	39	10 (25.64)	29 (74.36)	NC (NC, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.1: PlexiQoL - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	36	6 (16.67)	30 (83.33)	NC (NC, NC)	0.57	(0.20, 1.63)	0.273
	Placebo N=74	32	9 (28.13)	23 (71.88)	NC (330.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.2: PlexiQoL - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	30	7 (23.33)	23 (76.67)	NC (339.00, NC)	0.57	(0.22, 1.50)	0.454	0.199
	Placebo N=74	41	12 (29.27)	29 (70.73)	NC (336.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.2: PlexiQoL - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	34	9 (26.47)	25 (73.53)	NC (337.00, NC)	1.36	(0.49, 3.77)	0.570
	Placebo N=74	30	7 (23.33)	23 (76.67)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.3: PlexiQoL - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	19	7 (36.84)	12 (63.16)	339.00 (225.00, NC)	0.78	(0.28, 2.21)	0.977	0.998
	Placebo N=74	22	8 (36.36)	14 (63.64)	NC (329.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 20.5.1.3: PlexiQoL - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	35	8 (22.86)	27 (77.14)	NC (NC, NC)	0.90	(0.36, 2.25)	0.772
	Placebo N=74	41	11 (26.83)	30 (73.17)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 20.5.1.3: PlexiQoL - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	4	0 (0.00)	4 (100)	NC (NC, NC)	NC	(NC, NC)	NC
	Placebo N=74	5	0 (0.00)	5 (100)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 20.5.1.4: PlexiQoL - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (56.00, NC)	0.22	(0.00, 299.1)	0.677	0.856
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (57.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 20.5.1.4: PlexiQoL - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	56	15 (26.79)	41 (73.21)	NC (339.00, NC)	0.90	(0.45, 1.79)	0.815
	Placebo N=74	61	18 (29.51)	43 (70.49)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 20.5.1.5: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	8	2 (25.00)	6 (75.00)	NC (57.00, NC)	2.34	(0.20, 26.86)	0.503	0.506
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (223.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.5: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	25	4 (16.00)	21 (84.00)	NC (NC, NC)	0.49	(0.15, 1.65)	0.290
	Placebo N=74	26	8 (30.77)	18 (69.23)	NC (329.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.5: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	17	7 (41.18)	10 (58.82)	339.00 (112.00, NC)	0.78	(0.28, 2.21)	0.999
	Placebo N=74	20	8 (40.00)	12 (60.00)	NC (222.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.5: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	14	3 (21.43)	11 (78.57)	NC (337.00, NC)	2.30	(0.36, 14.53)	0.503
	Placebo N=74	19	2 (10.53)	17 (89.47)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.6: PlexiQoL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	10 (90.91)	NC (112.00, NC)	0.26	(0.03, 2.42)	0.156	0.176
	Placebo N=74	18	6 (33.33)	12 (66.67)	NC (224.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.5.1.6: PlexiQoL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	12	3 (25.00)	9 (75.00)	NC (111.00, NC)	1.19	(0.19, 7.31)	0.943
	Placebo N=74	12	3 (25.00)	9 (75.00)	NC (223.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.5.1.6: PlexiQoL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	14	2 (14.29)	12 (85.71)	NC (NC, NC)	0.40	(0.08, 2.11)	0.164
	Placebo N=74	11	5 (45.45)	6 (54.55)	NC (57.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.5.1.6: PlexiQoL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	27	10 (37.04)	17 (62.96)	NC (225.00, NC)	2.03	(0.69, 6.02)	0.102
	Placebo N=74	29	5 (17.24)	24 (82.76)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 20.5.1.7: PlexiQoL - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	28	5 (17.86)	23 (82.14)	NC (NC, NC)	0.77	(0.17, 3.38)	0.968	0.652
	Placebo N=74	17	3 (17.65)	14 (82.35)	NC (NC, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.7: PlexiQoL - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	21	5 (23.81)	16 (76.19)	NC (337.00, NC)	0.74	(0.25, 2.24)	0.460
	Placebo N=74	25	9 (36.00)	16 (64.00)	NC (330.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.7: PlexiQoL - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	15	6 (40.00)	9 (60.00)	339.00 (60.00, NC)	1.39	(0.44, 4.35)	0.287
	Placebo N=74	29	7 (24.14)	22 (75.86)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.8: PlexiQoL - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	18	5 (27.78)	13 (72.22)	NC (225.00, NC)	0.87	(0.27, 2.84)	0.656	0.802
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (223.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.8: PlexiQoL - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	46	11 (23.91)	35 (76.09)	NC (339.00, NC)	0.79	(0.33, 1.89)	0.980
	Placebo N=74	51	12 (23.53)	39 (76.47)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.9: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	11	6 (54.55)	5 (45.45)	337.00 (56.00, NC)	0.89	(0.28, 2.81)	0.837	0.829
	Placebo N=74	12	6 (50.00)	6 (50.00)	336.00 (57.00, NC)				

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.9: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	6	1 (16.67)	5 (83.33)	NC (225.00, NC)	0.67	(0.06, 7.42)	0.721
	Placebo N=74	8	2 (25.00)	6 (75.00)	NC (221.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.9: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	28	5 (17.86)	23 (82.14)	NC (NC, NC)	0.66	(0.22, 2.02)	0.497
	Placebo N=74	29	8 (27.59)	21 (72.41)	NC (331.00, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 20.5.1.9: PlexiQoL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PlexiQoL	Selumetinib 25 mg/m2 BID N=71	19	4 (21.05)	15 (78.95)	NC (337.00, NC)	1.51	(0.33, 6.82)	0.599
	Placebo N=74	22	3 (13.64)	19 (86.36)	NC (NC, NC)			

PlexiQoL = Plexiform Neurofibroma Quality of Life scale; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 2.7 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.2.2 Endpunkt Gesundheitsbezogene Lebensqualität anhand PedsQL

1.2.2.1 Gesundheitsbezogene Lebensqualität anhand PedsQL – Zeit bis zur erstmaligen Verbesserung um ≥ 15 Punkte

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Table 19.2.1.1: PedsQL - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	28	12 (42.86)	16 (57.14)	NC (113.00, NC)	1.11	(0.52, 2.38)	0.738	0.603
	Placebo N=74	39	16 (41.03)	23 (58.97)	NC (224.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.1: PedsQL - Time to first improvement by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	37	22 (59.46)	15 (40.54)	114.00 (58.00, NC)	1.54	(0.78, 3.06)	0.290
	Placebo N=74	32	14 (43.75)	18 (56.25)	336.00 (61.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.2: PedsQL - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	31	17 (54.84)	14 (45.16)	224.00 (57.00, NC)	1.49	(0.74, 3.01)	0.262	0.570
	Placebo N=74	41	17 (41.46)	24 (58.54)	NC (113.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.2: PedsQL - Time to first improvement by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	34	17 (50.00)	17 (50.00)	226.00 (109.00, NC)	1.16	(0.54, 2.48)	0.537
	Placebo N=74	30	13 (43.33)	17 (56.67)	NC (112.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.3: PedsQL - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	20	8 (40.00)	12 (60.00)	NC (113.00, NC)	1.00	(0.34, 2.94)	0.833	0.851
	Placebo N=74	22	8 (36.36)	14 (63.64)	NC (58.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 19.2.1.3: PedsQL - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	35	20 (57.14)	15 (42.86)	113.00 (57.00, NC)	1.47	(0.78, 2.79)	0.235
	Placebo N=74	41	18 (43.90)	23 (56.10)	NC (112.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 19.2.1.3: PedsQL - Time to first improvement by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	4	2 (50.00)	2 (50.00)	NC (57.00, NC)	3.97	(0.26, 60.99)	0.850
	Placebo N=74	5	3 (60.00)	2 (40.00)	336.00 (57.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 19.2.1.4: PedsQL - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	2 (40.00)	109.00 (57.00, NC)	0.81	(0.15, 4.56)	0.617	0.528
	Placebo N=74	8	6 (75.00)	2 (25.00)	88.00 (56.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 19.2.1.4: PedsQL - Time to first improvement by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	57	29 (50.88)	28 (49.12)	232.00 (113.00, NC)	1.49	(0.86, 2.58)	0.141
	Placebo N=74	61	23 (37.70)	38 (62.30)	NC (232.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 19.2.1.5: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	9	5 (55.56)	4 (44.44)	232.00 (53.00, NC)	1.35	(0.32, 5.69)	0.675	0.965
	Placebo N=74	6	3 (50.00)	3 (50.00)	337.00 (57.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.5: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	25	14 (56.00)	11 (44.00)	222.00 (57.00, NC)	1.38	(0.62, 3.07)	0.386
	Placebo N=74	26	11 (42.31)	15 (57.69)	NC (61.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.5: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (56.00, NC)	1.36	(0.42, 4.36)	0.914
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (58.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.5: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	14	9 (64.29)	5 (35.71)	112.00 (57.00, NC)	1.54	(0.59, 4.00)	0.297
	Placebo N=74	19	9 (47.37)	10 (52.63)	336.00 (112.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.6: PedsQL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	11	6 (54.55)	5 (45.45)	107.00 (55.00, NC)	1.53	(0.50, 4.63)	0.428	0.658
	Placebo N=74	18	8 (44.44)	10 (55.56)	NC (57.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.2.1.6: PedsQL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	12	7 (58.33)	5 (41.67)	225.00 (56.00, NC)	1.07	(0.28, 4.00)	0.298
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (57.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.2.1.6: PedsQL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	15	7 (46.67)	8 (53.33)	NC (58.00, NC)	1.59	(0.24, 10.66)	0.187
	Placebo N=74	11	2 (18.18)	9 (81.82)	NC (105.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.2.1.6: PedsQL - Time to first improvement by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	27	14 (51.85)	13 (48.15)	222.00 (57.00, NC)	1.06	(0.51, 2.20)	0.920
	Placebo N=74	29	16 (55.17)	13 (44.83)	232.00 (60.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.2.1.7: PedsQL - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	13 (46.43)	114.00 (107.00, NC)	1.13	(0.46, 2.79)	0.823	0.285
	Placebo N=74	17	8 (47.06)	9 (52.94)	336.00 (57.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.7: PedsQL - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	21	14 (66.67)	7 (33.33)	58.00 (56.00, NC)	2.07	(0.93, 4.59)	0.060
	Placebo N=74	25	11 (44.00)	14 (56.00)	NC (112.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.7: PedsQL - Time to first improvement by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	16	5 (31.25)	11 (68.75)	NC (109.00, NC)	0.69	(0.24, 2.03)	0.611
	Placebo N=74	29	11 (37.93)	18 (62.07)	NC (112.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.8: PedsQL - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	18	9 (50.00)	9 (50.00)	222.00 (107.00, NC)	4.14	(1.09, 15.69)	0.022	0.072
	Placebo N=74	20	3 (15.00)	17 (85.00)	NC (NC, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.8: PedsQL - Time to first improvement by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	47	25 (53.19)	22 (46.81)	226.00 (58.00, NC)	1.10	(0.63, 1.90)	0.893
	Placebo N=74	51	27 (52.94)	24 (47.06)	232.00 (105.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.9: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	11	6 (54.55)	5 (45.45)	224.00 (55.00, NC)	2.91	(0.66, 12.82)	0.270	0.930
	Placebo N=74	12	4 (33.33)	8 (66.67)	NC (57.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.9: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	6	0 (0.00)	6 (100)	NC (NC, NC)	NC	(NC, NC)	0.107
	Placebo N=74	8	3 (37.50)	5 (62.50)	NC (56.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.9: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	28	15 (53.57)	13 (46.43)	222.00 (58.00, NC)	1.28	(0.61, 2.69)	0.500
	Placebo N=74	29	13 (44.83)	16 (55.17)	NC (62.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.2.1.9: PedsQL - Time to first improvement by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	20	13 (65.00)	7 (35.00)	112.00 (56.00, NC)	1.54	(0.67, 3.56)	0.211
	Placebo N=74	22	10 (45.45)	12 (54.55)	337.00 (64.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first improvement is time from randomisation to first improvement by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no improvement are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.2.2.2 Gesundheitsbezogene Lebensqualität anhand PedsQL – Zeit bis zur erstmaligen Verschlechterung um ≥ 15 Punkte

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Table 19.5.1.1: PedsQL - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 18 - <30

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	28	6 (21.43)	22 (78.57)	NC (NC, NC)	0.97	(0.33, 2.81)	0.844	0.928
	Placebo N=74	39	9 (23.08)	30 (76.92)	NC (NC, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.1: PedsQL - Time to first deterioration by >=15% scale range by Age Group (Full Analysis Set)
Age Group: 30 - <65

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	37	12 (32.43)	25 (67.57)	344.00 (338.00, NC)	0.99	(0.41, 2.38)	0.917
	Placebo N=74	32	9 (28.13)	23 (71.88)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.2: PedsQL - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Male

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	31	10 (32.26)	21 (67.74)	NC (336.00, NC)	0.96	(0.42, 2.17)	0.695	0.408
	Placebo N=74	41	14 (34.15)	27 (65.85)	NC (223.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.2: PedsQL - Time to first deterioration by >=15% scale range by Sex (Full Analysis Set)
Sex: Female

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	34	8 (23.53)	26 (76.47)	NC (338.00, NC)	1.66	(0.46, 5.96)	0.319
	Placebo N=74	30	4 (13.33)	26 (86.67)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.3: PedsQL - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Asian

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	20	6 (30.00)	14 (70.00)	NC (218.00, NC)	2.80	(0.69, 11.43)	0.223	0.391
	Placebo N=74	22	3 (13.64)	19 (86.36)	NC (NC, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 19.5.1.3: PedsQL - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: White

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	35	10 (28.57)	25 (71.43)	344.00 (338.00, NC)	0.95	(0.41, 2.19)	0.908
	Placebo N=74	41	12 (29.27)	29 (70.73)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 19.5.1.3: PedsQL - Time to first deterioration by >=15% scale range by Race (Full Analysis Set)
Race: Other

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	4	0 (0.00)	4 (100)	NC (NC, NC)	NC	(NC, NC)	0.180
	Placebo N=74	5	2 (40.00)	3 (60.00)	NC (56.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 19.5.1.4: PedsQL - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Hispanic or Latino

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	4 (80.00)	NC (57.00, NC)	1.97	(0.11, 35.83)	0.774	0.956
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (56.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 19.5.1.4: PedsQL - Time to first deterioration by >=15% scale range by Ethnicity (Full Analysis Set)
Ethnicity: Not Hispanic or Latino

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	57	17 (29.82)	40 (70.18)	344.00 (338.00, NC)	1.19	(0.60, 2.36)	0.724
	Placebo N=74	61	16 (26.23)	45 (73.77)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subjects with missing ethnicity are excluded.
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Table 19.5.1.5: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: North America

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	9	2 (22.22)	7 (77.78)	NC (57.00, NC)	0.66	(0.04, 10.39)	0.802	0.321
	Placebo N=74	6	1 (16.67)	5 (83.33)	NC (58.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.5: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	25	7 (28.00)	18 (72.00)	344.00 (338.00, NC)	0.59	(0.23, 1.53)	0.267
	Placebo N=74	26	11 (42.31)	15 (57.69)	NC (113.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.5: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Asia

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	17	6 (35.29)	11 (64.71)	NC (113.00, NC)	2.80	(0.69, 11.43)	0.174
	Placebo N=74	20	3 (15.00)	17 (85.00)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.5: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Full Analysis Set)
Geographical Region: Rest of the world

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	14	3 (21.43)	11 (78.57)	NC (113.00, NC)	1.27	(0.25, 6.34)	0.835
	Placebo N=74	19	3 (15.79)	16 (84.21)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.6: PedsQL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Extremity

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	8 (72.73)	344.00 (112.00, NC)	0.44	(0.07, 2.80)	0.337	0.390
	Placebo N=74	18	6 (33.33)	12 (66.67)	NC (107.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.5.1.6: PedsQL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Head/Neck

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	12	2 (16.67)	10 (83.33)	NC (338.00, NC)	0.46	(0.05, 3.94)	0.998
	Placebo N=74	12	2 (16.67)	10 (83.33)	NC (114.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.5.1.6: PedsQL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk/Extremity

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	15	4 (26.67)	11 (73.33)	NC (57.00, NC)	0.94	(0.17, 5.35)	0.397
	Placebo N=74	11	5 (45.45)	6 (54.55)	NC (57.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.5.1.6: PedsQL - Time to first deterioration by >=15% scale range by Target PN Location (Full Analysis Set)
Target PN Location: Trunk

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	27	9 (33.33)	18 (66.67)	NC (117.00, NC)	2.01	(0.66, 6.10)	0.194
	Placebo N=74	29	5 (17.24)	24 (82.76)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Subject with target PN location 'Other' is excluded.
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Table 19.5.1.7: PedsQL - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 0 - < 54

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	28	9 (32.14)	19 (67.86)	NC (117.00, NC)	1.89	(0.50, 7.09)	0.290	0.497
	Placebo N=74	17	3 (17.65)	14 (82.35)	NC (231.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.7: PedsQL - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: 54 - < 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	21	5 (23.81)	16 (76.19)	NC (338.00, NC)	0.79	(0.25, 2.50)	0.676
	Placebo N=74	25	7 (28.00)	18 (72.00)	NC (110.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.7: PedsQL - Time to first deterioration by >=15% scale range by Baseline Target PN Volume (Full Analysis Set)
Baseline Target PN Volume: >= 333

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	16	4 (25.00)	12 (75.00)	344.00 (NC, NC)	0.59	(0.15, 2.27)	0.550
	Placebo N=74	29	8 (27.59)	21 (72.41)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.8: PedsQL - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	18	2 (11.11)	16 (88.89)	NC (NC, NC)	0.23	(0.04, 1.21)	0.121	0.068
	Placebo N=74	20	7 (35.00)	13 (65.00)	NC (113.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.8: PedsQL - Time to first deterioration by >=15% scale range by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Full Analysis Set)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	47	16 (34.04)	31 (65.96)	NC (338.00, NC)	1.58	(0.73, 3.44)	0.266
	Placebo N=74	51	11 (21.57)	40 (78.43)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment and Geographical Region as fixed effects and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.9: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: China

						Comparison of treatment groups			
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]	Interaction p-value [d]
PedsQL	Selumetinib 25 mg/m2 BID N=71	11	2 (18.18)	9 (81.82)	NC (336.00, NC)	0.96	(0.13, 7.03)	0.927	0.287
	Placebo N=74	12	2 (16.67)	10 (83.33)	NC (110.00, NC)				

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
[d] p-value for interaction between treatment and subgroup factors using above Cox Proportional Hazards Model including interaction for treatment and subgroup.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.9: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Japan

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	6	4 (66.67)	2 (33.33)	165.50 (53.00, NC)	6.98	(0.77, 62.85)	0.043
	Placebo N=74	8	1 (12.50)	7 (87.50)	NC (57.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score. Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test. The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available. Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.9: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Europe

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	28	8 (28.57)	20 (71.43)	344.00 (338.00, NC)	0.68	(0.27, 1.71)	0.413
	Placebo N=74	29	11 (37.93)	18 (62.07)	NC (114.00, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Table 19.5.1.9: PedsQL - Time to first deterioration by >=15% scale range by Geographical Region (Stratification Factor) (Full Analysis Set)
Geographical Region: Rest of World

						Comparison of treatment groups		
	Treatment group	n	Subjects with event Number (%)	Subjects censored Number (%)	Median time to event (days), 95% CI [a]	Hazard ratio (HR) [b]	95% CI [b]	p-value [c]
PedsQL	Selumetinib 25 mg/m2 BID N=71	20	4 (20.00)	16 (80.00)	NC (NC, NC)	0.94	(0.23, 3.82)	0.999
	Placebo N=74	22	4 (18.18)	18 (81.82)	NC (NC, NC)			

PedsQL = Paediatric Quality of Life Inventory; CI = Confidence interval
Time to first deterioration is time from randomisation to first deterioration by at least 15% scale range, ie by at least a score of 15 points, compared with the baseline score.
Subjects with no deterioration are censored at the day of last non-missing visit available during randomised period.
[a] Calculated using the Kaplan-Meier technique [b] Analysis is based on a Cox Proportional Hazards Regression Model. [c] The p-value is based on an unstratified log-rank test.
The Cox Proportional Hazards Model includes Treatment as fixed effect and baseline chronic target PN pain intensity score as a covariate.
PN = Plexiform neurofibroma
N = Number of subjects in treatment group from full analysis set; n = Number of subjects in category/analysis with baseline and at least one post-baseline measurement available.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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1.3 Endpunktkategorie Sicherheit

1.3.1 Endpunkt Unerwünschte Ereignisse (UE)

1.3.1.1 UE jeglichen Schweregrads

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Table 21.2.1.1 Patients with AE by Age Group (Randomised Period SAF)
Age Group: 18 - <30

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	32 (100.0%)	NC (NC, NC)	1.05 (0.98, 1.12)	0.05 (-0.02, 0.11)	0.502	0.260
Placebo N=74	42	40 (95.2%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.1 Patients with AE by Age Group (Randomised Period SAF)
Age Group: 30 - <65

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	39 (100.0%)	NC (NC, NC)	1.14 (1.00, 1.30)	0.13 (0.01, 0.24)	0.037
Placebo N=74	32	28 (87.5%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.2 Patients with AE by Sex (Randomised Period SAF)
Sex: Male

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	33 (100.0%)	NC (NC, NC)	1.11 (1.00, 1.22)	0.10 (0.01, 0.18)	0.126	0.600
Placebo N=74	42	38 (90.5%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.2 Patients with AE by Sex (Randomised Period SAF)
Sex: Female

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	38 (100.0%)	NC (NC, NC)	1.07 (0.98, 1.17)	0.06 (-0.02, 0.15)	0.205
Placebo N=74	32	30 (93.8%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.3 Patients with AE by Race (Randomised Period SAF)
Race: Asian

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	22 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC	NC#
Placebo N=74	23	23 (100.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.2.1.3 Patients with AE by Race (Randomised Period SAF)
Race: White

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	38 (100.0%)	NC (NC, NC)	1.13 (1.02, 1.26)	0.12 (0.02, 0.21)	0.057
Placebo N=74	43	38 (88.4%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.2.1.3 Patients with AE by Race (Randomised Period SAF)
Race: Other

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	5 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC
Placebo N=74	5	5 (100.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.2.1.4 Patients with AE by Ethnicity (Randomised Period SAF)
Ethnicity: Hispanic or Latino

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	5 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC	NC#
Placebo N=74	9	9 (100.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subjects with missing ethnicity are excluded.
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Table 21.2.1.4 Patients with AE by Ethnicity (Randomised Period SAF)
Ethnicity: Not Hispanic or Latino

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	63 (100.0%)	NC (NC, NC)	1.11 (1.02, 1.20)	0.10 (0.02, 0.17)	0.028
Placebo N=74	63	57 (90.5%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subjects with missing ethnicity are excluded.
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Table 21.2.1.5 Patients with AE by Geographical Region (Randomised Period SAF)
Geographical Region: North America

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	9 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC	0.240
Placebo N=74	6	6 (100.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
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Table 21.2.1.5 Patients with AE by Geographical Region (Randomised Period SAF)
Geographical Region: Europe

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	27 (100.0%)	NC (NC, NC)	1.08 (0.97, 1.20)	0.07 (-0.02, 0.17)	0.491
Placebo N=74	27	25 (92.6%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.5 Patients with AE by Geographical Region (Randomised Period SAF)
Geographical Region: Asia

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	18 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC
Placebo N=74	21	21 (100.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
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Table 21.2.1.5 Patients with AE by Geographical Region (Randomised Period SAF)
Geographical Region: Rest of the world

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	17 (100.0%)	NC (NC, NC)	1.25 (1.00, 1.56)	0.20 (0.02, 0.38)	0.109
Placebo N=74	20	16 (80.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.6 Patients with AE by Target PN Location (Randomised Period SAF)
Target PN Location: Extremity

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	13 (100.0%)	NC (NC, NC)	1.13 (0.96, 1.32)	0.11 (-0.03, 0.26)	0.497	0.220
Placebo N=74	18	16 (88.9%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.2.1.6 Patients with AE by Target PN Location (Randomised Period SAF)
Target PN Location: Head/Neck

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	12 (100.0%)	NC (NC, NC)	1.33 (0.96, 1.85)	0.25 (0.01, 0.49)	0.217
Placebo N=74	12	9 (75.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.2.1.6 Patients with AE by Target PN Location (Randomised Period SAF)
Target PN Location: Trunk/Extremity

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	16 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC
Placebo N=74	11	11 (100.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
Subject with target PN location 'Other' is excluded.
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Table 21.2.1.6 Patients with AE by Target PN Location (Randomised Period SAF)
Target PN Location: Trunk

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	30 (100.0%)	NC (NC, NC)	1.03 (0.97, 1.10)	0.03 (-0.03, 0.09)	1.000
Placebo N=74	32	31 (96.9%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.2.1.7 Patients with AE by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: 0 - < 54

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	29 (100.0%)	NC (NC, NC)	1.06 (0.95, 1.17)	0.05 (-0.05, 0.15)	0.396	0.325
Placebo N=74	19	18 (94.7%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.7 Patients with AE by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: 54 - < 333

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	24 (100.0%)	NC (NC, NC)	1.19 (1.00, 1.41)	0.16 (0.02, 0.30)	0.110
Placebo N=74	25	21 (84.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.7 Patients with AE by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: >= 333

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	18 (100.0%)	NC (NC, NC)	1.03 (0.97, 1.11)	0.03 (-0.03, 0.10)	1.000
Placebo N=74	30	29 (96.7%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.8 Patients with AE by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	21 (100.0%)	NC (NC, NC)	1.24 (1.00, 1.52)	0.19 (0.02, 0.36)	0.107	0.114
Placebo N=74	21	17 (81.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.8 Patients with AE by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	50 (100.0%)	NC (NC, NC)	1.04 (0.99, 1.10)	0.04 (-0.01, 0.09)	0.496
Placebo N=74	53	51 (96.2%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.9 Patients with AE by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: China

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	11 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC	0.734
Placebo N=74	13	13 (100.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
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Table 21.2.1.9 Patients with AE by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Japan

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	7 (100.0%)	NC (NC, NC)	NC (NC, NC)	NC (NC, NC)	NC
Placebo N=74	8	8 (100.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
RR, RD and p-values are NC as event percentage is 100% across both treatment groups.
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Table 21.2.1.9 Patients with AE by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Europe

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	31 (100.0%)	NC (NC, NC)	1.11 (0.99, 1.25)	0.10 (-0.01, 0.21)	0.113
Placebo N=74	30	27 (90.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.2.1.9 Patients with AE by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Rest of World

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	22 (100.0%)	NC (NC, NC)	1.15 (0.98, 1.35)	0.13 (-0.01, 0.27)	0.233
Placebo N=74	23	20 (87.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.9 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: China

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	3 (27.3%)	4.50 (0.39, 51.30)	3.55 (0.43, 29.42)	0.20 (-0.10, 0.50)	0.300	0.757
Placebo N=74	13	1 (7.7%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.9 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Japan

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	1 (14.3%)	NC (NC, NC)	NC (NC, NC)	0.14 (-0.12, 0.40)	0.467
Placebo N=74	8	0 (0.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.9 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Europe

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	9 (29.0%)	1.34 (0.43, 4.24)	1.24 (0.53, 2.91)	0.06 (-0.16, 0.28)	0.772
Placebo N=74	30	7 (23.3%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.9 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Rest of World

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	10 (45.5%)	3.00 (0.82, 10.99)	2.09 (0.85, 5.15)	0.24 (-0.03, 0.50)	0.120
Placebo N=74	23	5 (21.7%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.1 Patients with Severe AE (CTCAE >= 3) by Age Group (Randomised Period SAF)
Age Group: 18 - <30

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	10 (31.3%)	2.27 (0.75, 6.85)	1.88 (0.80, 4.38)	0.15 (-0.05, 0.34)	0.169	0.931
Placebo N=74	42	7 (16.7%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.1 Patients with Severe AE (CTCAE >= 3) by Age Group (Randomised Period SAF)
Age Group: 30 - <65

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	13 (33.3%)	2.17 (0.71, 6.57)	1.78 (0.76, 4.15)	0.15 (-0.05, 0.35)	0.190
Placebo N=74	32	6 (18.8%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.2 Patients with Severe AE (CTCAE >= 3) by Sex (Randomised Period SAF)
Sex: Male

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	9 (27.3%)	1.38 (0.47, 3.98)	1.27 (0.57, 2.84)	0.06 (-0.14, 0.25)	0.595	0.201
Placebo N=74	42	9 (21.4%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.2 Patients with Severe AE (CTCAE >= 3) by Sex (Randomised Period SAF)
Sex: Female

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	14 (36.8%)	4.08 (1.18, 14.08)	2.95 (1.08, 8.07)	0.24 (0.05, 0.43)	0.028
Placebo N=74	32	4 (12.5%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.3 Patients with Severe AE (CTCAE >= 3) by Race (Randomised Period SAF)
Race: Asian

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	4 (18.2%)	4.89 (0.50, 47.71)	4.18 (0.51, 34.56)	0.14 (-0.04, 0.32)	0.187	0.625
Placebo N=74	23	1 (4.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.8.1.3 Patients with Severe AE (CTCAE >= 3) by Race (Randomised Period SAF)
Race: White

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	15 (39.5%)	1.90 (0.74, 4.88)	1.54 (0.81, 2.94)	0.14 (-0.06, 0.34)	0.235
Placebo N=74	43	11 (25.6%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.8.1.3 Patients with Severe AE (CTCAE >= 3) by Race (Randomised Period SAF)
Race: Other

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.0%)	1.00 (0.05, 22.18)	1.00 (0.08, 11.93)	0.00 (-0.50, 0.50)	1.000
Placebo N=74	5	1 (20.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:20

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Table 21.8.1.4 Patients with Severe AE (CTCAE >= 3) by Ethnicity (Randomised Period SAF)
Ethnicity: Hispanic or Latino

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.0%)	0.50 (0.04, 6.68)	0.60 (0.08, 4.35)	-0.13 (-0.60, 0.33)	1.000	0.223
Placebo N=74	9	3 (33.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
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Table 21.8.1.4 Patients with Severe AE (CTCAE >= 3) by Ethnicity (Randomised Period SAF)
Ethnicity: Not Hispanic or Latino

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	22 (34.9%)	2.84 (1.21, 6.66)	2.20 (1.14, 4.26)	0.19 (0.04, 0.34)	0.023
Placebo N=74	63	10 (15.9%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
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Table 21.8.1.5 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Randomised Period SAF)
Geographical Region: North America

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	3 (33.3%)	2.50 (0.19, 32.19)	2.00 (0.27, 14.98)	0.17 (-0.26, 0.60)	0.604	0.548
Placebo N=74	6	1 (16.7%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.5 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Randomised Period SAF)
Geographical Region: Europe

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	8 (29.6%)	1.20 (0.36, 3.97)	1.14 (0.48, 2.71)	0.04 (-0.20, 0.28)	1.000
Placebo N=74	27	7 (25.9%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.5 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Randomised Period SAF)
Geographical Region: Asia

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	4 (22.2%)	5.71 (0.58, 56.73)	4.67 (0.57, 38.07)	0.17 (-0.04, 0.39)	0.162
Placebo N=74	21	1 (4.8%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.5 Patients with Severe AE (CTCAE >= 3) by Geographical Region (Randomised Period SAF)
Geographical Region: Rest of the world

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	8 (47.1%)	3.56 (0.83, 15.18)	2.35 (0.86, 6.47)	0.27 (-0.02, 0.57)	0.157
Placebo N=74	20	4 (20.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.6 Patients with Severe AE (CTCAE >= 3) by Target PN Location (Randomised Period SAF)
Target PN Location: Extremity

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	3 (23.1%)	5.10 (0.47, 55.89)	4.15 (0.48, 35.58)	0.18 (-0.08, 0.43)	0.284	0.240
Placebo N=74	18	1 (5.6%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.8.1.6 Patients with Severe AE (CTCAE >= 3) by Target PN Location (Randomised Period SAF)
Target PN Location: Head/Neck

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	6 (50.0%)	11.00 (1.06, 114.09)	6.00 (0.85, 42.59)	0.42 (0.09, 0.74)	0.069
Placebo N=74	12	1 (8.3%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.8.1.6 Patients with Severe AE (CTCAE >= 3) by Target PN Location (Randomised Period SAF)
Target PN Location: Trunk/Extremity

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	6 (37.5%)	2.70 (0.43, 16.94)	2.06 (0.51, 8.40)	0.19 (-0.14, 0.52)	0.405
Placebo N=74	11	2 (18.2%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.8.1.6 Patients with Severe AE (CTCAE >= 3) by Target PN Location (Randomised Period SAF)
Target PN Location: Trunk

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	8 (26.7%)	0.93 (0.30, 2.84)	0.95 (0.42, 2.14)	-0.01 (-0.24, 0.21)	1.000
Placebo N=74	32	9 (28.1%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.8.1.7 Patients with Severe AE (CTCAE >= 3) by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: 0 - < 54

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	6 (20.7%)	0.57 (0.15, 2.12)	0.66 (0.25, 1.73)	-0.11 (-0.36, 0.15)	0.501	0.047
Placebo N=74	19	6 (31.6%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.7 Patients with Severe AE (CTCAE >= 3) by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: 54 - < 333

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	10 (41.7%)	3.75 (0.98, 14.35)	2.60 (0.94, 7.19)	0.26 (0.01, 0.50)	0.062
Placebo N=74	25	4 (16.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.7 Patients with Severe AE (CTCAE >= 3) by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: >= 333

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	7 (38.9%)	5.73 (1.25, 26.28)	3.89 (1.15, 13.17)	0.29 (0.04, 0.54)	0.027
Placebo N=74	30	3 (10.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.8 Patients with Severe AE (CTCAE >= 3) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	9 (42.9%)	15.00 (1.68, 133.55)	9.00 (1.25, 64.89)	0.38 (0.15, 0.61)	0.009	0.062
Placebo N=74	21	1 (4.8%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.8.1.8 Patients with Severe AE (CTCAE >= 3) by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	14 (28.0%)	1.33 (0.54, 3.24)	1.24 (0.63, 2.41)	0.05 (-0.11, 0.22)	0.651
Placebo N=74	53	12 (22.6%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.1.3 Schwerwiegende unerwünschte Ereignisse (SUE)

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Table 21.4.1.1 Patients with Serious Adverse Event by Age Group (Randomised Period SAF)
Age Group: 18 - <30

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	3 (9.4%)	0.62 (0.14, 2.70)	0.66 (0.18, 2.43)	-0.05 (-0.20, 0.10)	0.723	0.249
Placebo N=74	42	6 (14.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.1 Patients with Serious Adverse Event by Age Group (Randomised Period SAF)
Age Group: 30 - <65

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	7 (17.9%)	2.11 (0.50, 8.95)	1.91 (0.54, 6.81)	0.09 (-0.07, 0.24)	0.495
Placebo N=74	32	3 (9.4%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.2 Patients with Serious Adverse Event by Sex (Randomised Period SAF)
Sex: Male

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	5 (15.2%)	1.07 (0.30, 3.87)	1.06 (0.35, 3.17)	0.01 (-0.15, 0.17)	1.000	0.752
Placebo N=74	42	6 (14.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.2 Patients with Serious Adverse Event by Sex (Randomised Period SAF)
Sex: Female

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	5 (13.2%)	1.46 (0.32, 6.67)	1.40 (0.36, 5.42)	0.04 (-0.11, 0.19)	0.719
Placebo N=74	32	3 (9.4%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.3 Patients with Serious Adverse Event by Race (Randomised Period SAF)
Race: Asian

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	1 (4.5%)	1.05 (0.06, 17.85)	1.05 (0.07, 15.70)	0.00 (-0.12, 0.12)	1.000	0.957
Placebo N=74	23	1 (4.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:35:56

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Table 21.4.1.3 Patients with Serious Adverse Event by Race (Randomised Period SAF)
Race: White

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	8 (21.1%)	1.17 (0.39, 3.49)	1.13 (0.47, 2.72)	0.02 (-0.15, 0.20)	0.788
Placebo N=74	43	8 (18.6%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.4.1.4 Patients with Serious Adverse Event by Ethnicity (Randomised Period SAF)
Ethnicity: Not Hispanic or Latino

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	63	10 (15.9%)	1.13 (0.43, 3.01)	1.11 (0.48, 2.55)	0.02 (-0.11, 0.14)	1.000	NC#
Placebo N=74	63	9 (14.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subjects with missing ethnicity are excluded.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:35:57

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Table 21.4.1.5 Patients with Serious Adverse Event by Geographical Region (Randomised Period SAF)
Geographical Region: North America

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	3 (33.3%)	NC (NC, NC)	NC (NC, NC)	0.33 (0.03, 0.64)	0.229	0.737
Placebo N=74	6	0 (0.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.5 Patients with Serious Adverse Event by Geographical Region (Randomised Period SAF)
Geographical Region: Europe

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	4 (14.8%)	0.50 (0.13, 1.95)	0.57 (0.19, 1.73)	-0.11 (-0.32, 0.10)	0.501
Placebo N=74	27	7 (25.9%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.5 Patients with Serious Adverse Event by Geographical Region (Randomised Period SAF)
Geographical Region: Asia

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	1 (5.6%)	1.18 (0.07, 20.26)	1.17 (0.08, 17.35)	0.01 (-0.13, 0.15)	1.000
Placebo N=74	21	1 (4.8%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.5 Patients with Serious Adverse Event by Geographical Region (Randomised Period SAF)
Geographical Region: Rest of the world

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	2 (11.8%)	2.53 (0.21, 30.68)	2.35 (0.23, 23.75)	0.07 (-0.11, 0.25)	0.584
Placebo N=74	20	1 (5.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.6 Patients with Serious Adverse Event by Target PN Location (Randomised Period SAF)
Target PN Location: Extremity

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	2 (15.4%)	3.09 (0.25, 38.32)	2.77 (0.28, 27.40)	0.10 (-0.12, 0.32)	0.558	0.656
Placebo N=74	18	1 (5.6%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.4.1.6 Patients with Serious Adverse Event by Target PN Location (Randomised Period SAF)
Target PN Location: Head/Neck

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	1 (8.3%)	NC (NC, NC)	NC (NC, NC)	0.08 (-0.07, 0.24)	1.000
Placebo N=74	12	0 (0.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.4.1.6 Patients with Serious Adverse Event by Target PN Location (Randomised Period SAF)
Target PN Location: Trunk/Extremity

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	1 (6.3%)	0.30 (0.02, 3.80)	0.34 (0.04, 3.34)	-0.12 (-0.38, 0.14)	0.549
Placebo N=74	11	2 (18.2%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.4.1.6 Patients with Serious Adverse Event by Target PN Location (Randomised Period SAF)
Target PN Location: Trunk

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	6 (20.0%)	1.08 (0.31, 3.82)	1.07 (0.39, 2.95)	0.01 (-0.18, 0.21)	1.000
Placebo N=74	32	6 (18.8%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 21.4.1.8 Patients with Serious Adverse Event by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	2 (9.5%)	2.11 (0.18, 25.17)	2.00 (0.20, 20.41)	0.05 (-0.11, 0.20)	1.000	0.617
Placebo N=74	21	1 (4.8%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:02

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Table 21.4.1.8 Patients with Serious Adverse Event by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	8 (16.0%)	1.07 (0.37, 3.11)	1.06 (0.43, 2.61)	0.01 (-0.13, 0.15)	1.000
Placebo N=74	53	8 (15.1%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.4.1.9 Patients with Serious Adverse Event by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: China

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	1 (9.1%)	1.20 (0.07, 21.72)	1.18 (0.08, 16.78)	0.01 (-0.21, 0.24)	1.000	0.171
Placebo N=74	13	1 (7.7%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 21.4.1.9 Patients with Serious Adverse Event by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Europe

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	4 (12.9%)	0.49 (0.13, 1.87)	0.55 (0.18, 1.70)	-0.10 (-0.30, 0.09)	0.335
Placebo N=74	30	7 (23.3%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 21.4.1.9 Patients with Serious Adverse Event by Geographical Region (Stratification Factor) (Randomised Period SAF)
Geographical Region: Rest of World

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	5 (22.7%)	6.47 (0.69, 60.68)	5.23 (0.66, 41.26)	0.18 (-0.01, 0.38)	0.096
Placebo N=74	23	1 (4.3%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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1.3.1.4 Abbruch der Studienmedikation aufgrund von UE

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Table 21.12.1.8 Patients with AE Leading to Permanent Discontinuation of Study Drug by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	2 (9.5%)	NC (NC, NC)	NC (NC, NC)	0.10 (-0.03, 0.22)	0.488	1.000
Placebo N=74	21	0 (0.0%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.12.1.8 Patients with AE Leading to Permanent Discontinuation of Study Drug by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	7 (14.0%)	1.56 (0.46, 5.29)	1.48 (0.50, 4.37)	0.05 (-0.08, 0.17)	0.548
Placebo N=74	53	5 (9.4%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.12.1.1 Patients with AE Leading to Permanent Discontinuation of Study Drug by Age Group (Randomised Period SAF)
Age Group: 18 - <30

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	2 (6.3%)	1.33 (0.18, 10.01)	1.31 (0.20, 8.82)	0.01 (-0.09, 0.12)	1.000	0.747
Placebo N=74	42	2 (4.8%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.12.1.1 Patients with AE Leading to Permanent Discontinuation of Study Drug by Age Group (Randomised Period SAF)
Age Group: 30 - <65

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	7 (17.9%)	2.11 (0.50, 8.95)	1.91 (0.54, 6.81)	0.09 (-0.07, 0.24)	0.495
Placebo N=74	32	3 (9.4%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.12.1.3 Patients with AE Leading to Permanent Discontinuation of Study Drug by Race (Randomised Period SAF)
Race: Asian

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	2 (9.1%)	2.20 (0.19, 26.16)	2.09 (0.20, 21.45)	0.05 (-0.10, 0.19)	0.608	0.876
Placebo N=74	23	1 (4.3%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.12.1.3 Patients with AE Leading to Permanent Discontinuation of Study Drug by Race (Randomised Period SAF)
Race: White

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	6 (15.8%)	1.83 (0.47, 7.04)	1.70 (0.52, 5.57)	0.06 (-0.08, 0.21)	0.503
Placebo N=74	43	4 (9.3%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in Randomized Period Safety Analysis Set
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Table 21.12.1.4 Patients with AE Leading to Permanent Discontinuation of Study Drug by Ethnicity (Randomised Period SAF)
Ethnicity: Not Hispanic or Latino

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	63	9 (14.3%)	1.93 (0.61, 6.13)	1.80 (0.64, 5.07)	0.06 (-0.05, 0.17)	0.396	NC#
Placebo N=74	63	5 (7.9%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
#P-value is not computable when events are present in only one of the subgroup factors or risk ratio is not computable.
Subjects with missing ethnicity are excluded.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:38

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Table 21.12.1.7 Patients with AE Leading to Permanent Discontinuation of Study Drug by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: 0 - < 54

			Comparison of treatment groups				
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	6 (20.7%)	0.98 (0.24, 4.06)	0.98 (0.32, 3.03)	0.00 (-0.24, 0.23)	1.000	0.940
Placebo N=74	19	4 (21.1%)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.12.1.7 Patients with AE Leading to Permanent Discontinuation of Study Drug by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: 54 - < 333

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	2 (8.3%)	NC (NC, NC)	NC (NC, NC)	0.08 (-0.03, 0.19)	0.235
Placebo N=74	25	0 (0.0%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 21.12.1.7 Patients with AE Leading to Permanent Discontinuation of Study Drug by Baseline Target PN Volume (Randomised Period SAF)
Baseline Target PN Volume: >= 333

			Comparison of treatment groups			
Treatment Group	n	Subjects with Event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	1 (5.6%)	1.71 (0.10, 29.07)	1.67 (0.11, 25.04)	0.02 (-0.10, 0.15)	1.000
Placebo N=74	30	1 (3.3%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval
[a] Based on Fisher's exact test.
[b] Interaction p-value via Cochran's Q test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set; n = Number of subjects in treatment group within subgroup factor.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.2 UE nach System Organ Class (SOC) und Preferred Term (PT)

1.3.2.1 UE jeglichen Schweregrads

1.3.2.1.1 UE jeglichen Schweregrads – Alter

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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Gastrointestinal disorders
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	24 (75.00)	3.00 (1.10, 8.18)	1.50 (1.04, 2.16)	0.25 (0.04, 0.46)	0.034	0.253
Placebo N=74	42	21 (50.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Gastrointestinal disorders
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	29 (74.36)	5.54 (1.99, 15.42)	2.16 (1.30, 3.61)	0.40 (0.19, 0.61)	<0.001
Placebo N=74	32	11 (34.38)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	13 (40.63)	3.42 (1.17, 10.03)	2.44 (1.10, 5.40)	0.24 (0.04, 0.44)	0.034	0.198
Placebo N=74	42	7 (16.67)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	17 (43.59)	11.59 (2.42, 55.44)	6.97 (1.74, 27.96)	0.37 (0.20, 0.55)	<0.001
Placebo N=74	32	2 (6.25)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	10 (31.25)	2.73 (0.87, 8.55)	2.19 (0.89, 5.39)	0.17 (-0.02, 0.36)	0.094	1.000
Placebo N=74	42	6 (14.29)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	8 (20.51)	NC	NC	0.21 (0.08, 0.33)	0.007
Placebo N=74	32	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	30 (93.75)	24.38 (5.12, 116.11)	2.46 (1.66, 3.66)	0.56 (0.39, 0.73)	<0.001	0.709
Placebo N=74	42	16 (38.10)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	34 (87.18)	14.96 (4.51, 49.67)	2.79 (1.65, 4.73)	0.56 (0.37, 0.75)	<0.001
Placebo N=74	32	10 (31.25)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	20 (62.50)	10.00 (3.26, 30.71)	4.38 (1.99, 9.62)	0.48 (0.28, 0.68)	<0.001	0.369
Placebo N=74	42	6 (14.29)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	22 (56.41)	19.41 (4.06, 92.84)	9.03 (2.29, 35.52)	0.50 (0.32, 0.68)	<0.001
Placebo N=74	32	2 (6.25)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: General disorders and administration site conditions
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	15 (46.88)	2.49 (0.94, 6.61)	1.79 (0.96, 3.35)	0.21 (-0.01, 0.42)	0.087	0.931
Placebo N=74	42	11 (26.19)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: General disorders and administration site conditions
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	21 (53.85)	2.57 (0.97, 6.82)	1.72 (0.95, 3.11)	0.23 (0.00, 0.45)	0.092
Placebo N=74	32	10 (31.25)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Investigations
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	17 (53.13)	2.83 (1.08, 7.43)	1.86 (1.04, 3.32)	0.25 (0.03, 0.47)	0.054	0.506
Placebo N=74	42	12 (28.57)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Investigations
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	27 (69.23)	5.75 (2.06, 16.07)	2.46 (1.36, 4.45)	0.41 (0.20, 0.62)	<0.001
Placebo N=74	32	9 (28.13)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Investigations PT: Aspartate aminotransferase increased
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	7 (21.88)	2.66 (0.70, 10.04)	2.30 (0.74, 7.18)	0.12 (-0.05, 0.29)	0.191	1.000
Placebo N=74	42	4 (9.52)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Investigations PT: Aspartate aminotransferase increased
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	6 (15.38)	NC	NC	0.15 (0.04, 0.27)	0.029
Placebo N=74	32	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Age Group: 18 - <30

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	32	13 (40.63)	28.05 (3.42, 230.33)	17.06 (2.35, 123.74)	0.38 (0.21, 0.56)	<0.001	0.306
Placebo N=74	42	1 (2.38)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.1: Patients with AE by SOC and PT, by Age Group (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Age Group: 30 - <65

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	39	19 (48.72)	9.18 (2.39, 35.22)	5.20 (1.69, 16.00)	0.39 (0.21, 0.58)	<0.001
Placebo N=74	32	3 (9.38)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.2.1.2 UE jeglichen Schweregrads – Geschlecht

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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Gastrointestinal disorders
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	20 (60.61)	2.77 (1.08, 7.10)	1.70 (1.04, 2.77)	0.25 (0.03, 0.47)	0.038	0.903
Placebo N=74	42	15 (35.71)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Gastrointestinal disorders
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	33 (86.84)	5.82 (1.81, 18.75)	1.63 (1.15, 2.32)	0.34 (0.13, 0.54)	0.003
Placebo N=74	32	17 (53.13)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	13 (39.39)	4.81 (1.50, 15.44)	3.31 (1.31, 8.35)	0.27 (0.08, 0.47)	0.007	0.909
Placebo N=74	42	5 (11.90)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	17 (44.74)	5.67 (1.66, 19.34)	3.58 (1.34, 9.56)	0.32 (0.13, 0.52)	0.004
Placebo N=74	32	4 (12.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	3 (9.09)	2.00 (0.31, 12.73)	1.91 (0.34, 10.77)	0.04 (-0.07, 0.16)	0.649	0.621
Placebo N=74	42	2 (4.76)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	15 (39.47)	4.57 (1.33, 15.67)	3.16 (1.16, 8.56)	0.27 (0.08, 0.46)	0.015
Placebo N=74	32	4 (12.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	31 (93.94)	34.58 (7.18, 166.61)	3.03 (1.92, 4.81)	0.63 (0.47, 0.79)	<0.001	0.279
Placebo N=74	42	13 (30.95)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	33 (86.84)	9.65 (2.98, 31.26)	2.14 (1.38, 3.31)	0.46 (0.26, 0.66)	<0.001
Placebo N=74	32	13 (40.63)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	20 (60.61)	30.77 (6.32, 149.76)	12.73 (3.20, 50.60)	0.56 (0.38, 0.74)	<0.001	0.079
Placebo N=74	42	2 (4.76)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	22 (57.89)	5.96 (1.99, 17.84)	3.09 (1.43, 6.67)	0.39 (0.18, 0.60)	0.001
Placebo N=74	32	6 (18.75)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	6 (18.18)	NC	NC	0.18 (0.05, 0.31)	0.006	1.000
Placebo N=74	42	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	7 (18.42)	1.58 (0.42, 5.98)	1.47 (0.47, 4.58)	0.06 (-0.11, 0.23)	0.533
Placebo N=74	32	4 (12.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: General disorders and administration site conditions
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	14 (42.42)	3.68 (1.27, 10.69)	2.55 (1.16, 5.58)	0.26 (0.05, 0.46)	0.020	0.163
Placebo N=74	42	7 (16.67)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: General disorders and administration site conditions
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	22 (57.89)	1.77 (0.68, 4.57)	1.32 (0.82, 2.13)	0.14 (-0.09, 0.37)	0.337
Placebo N=74	32	14 (43.75)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Investigations
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	23 (69.70)	5.13 (1.91, 13.80)	2.25 (1.36, 3.73)	0.39 (0.18, 0.60)	0.001	0.965
Placebo N=74	42	13 (30.95)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Investigations
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	21 (55.26)	3.71 (1.33, 10.32)	2.21 (1.14, 4.30)	0.30 (0.08, 0.52)	0.015
Placebo N=74	32	8 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Investigations PT: Aspartate aminotransferase increased
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	6 (18.18)	2.11 (0.54, 8.21)	1.91 (0.59, 6.21)	0.09 (-0.07, 0.25)	0.320	1.000
Placebo N=74	42	4 (9.52)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Investigations PT: Aspartate aminotransferase increased
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	7 (18.42)	NC	NC	0.18 (0.06, 0.31)	0.013
Placebo N=74	32	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Sex: Male

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	33	20 (60.61)	14.62 (4.21, 50.74)	6.36 (2.41, 16.82)	0.51 (0.32, 0.70)	<0.001	1.000
Placebo N=74	42	4 (9.52)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.2: Patients with AE by SOC and PT, by Sex (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Sex: Female

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	12 (31.58)	NC	NC	0.32 (0.17, 0.46)	<0.001
Placebo N=74	32	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.2.1.3 UE jeglichen Schweregrads – Abstammung

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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	15 (68.18)	1.65 (0.49, 5.57)	1.21 (0.76, 1.91)	0.12 (-0.16, 0.40)	0.542	0.352
Placebo N=74	23	13 (56.52)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	28 (73.68)	4.28 (1.66, 11.03)	1.86 (1.23, 2.82)	0.34 (0.14, 0.54)	0.003
Placebo N=74	43	17 (39.53)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	6.00 (0.35, 101.57)	2.00 (0.63, 6.38)	0.40 (-0.15, 0.95)	0.524
Placebo N=74	5	2 (40.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	10 (45.45)	3.96 (1.01, 15.52)	2.61 (0.96, 7.11)	0.28 (0.02, 0.54)	0.057	0.986
Placebo N=74	23	4 (17.39)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	13 (34.21)	3.95 (1.25, 12.46)	2.94 (1.16, 7.49)	0.23 (0.05, 0.40)	0.018
Placebo N=74	43	5 (11.63)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	NC	NC	0.40 (-0.03, 0.83)	0.444
Placebo N=74	5	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	0 (0.00)	NC	NC	-0.04 (-0.13, 0.04)	1.000	1.000
Placebo N=74	23	1 (4.35)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	11 (28.95)	3.10 (0.96, 9.94)	2.49 (0.95, 6.52)	0.17 (0.00, 0.35)	0.091
Placebo N=74	43	5 (11.63)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	NC	NC	0.40 (-0.03, 0.83)	0.444
Placebo N=74	5	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	21 (95.45)	39.38 (4.44, 348.98)	2.74 (1.56, 4.84)	0.61 (0.39, 0.82)	<0.001	0.741
Placebo N=74	23	8 (34.78)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	34 (89.47)	13.00 (3.90, 43.29)	2.26 (1.54, 3.33)	0.50 (0.32, 0.68)	<0.001
Placebo N=74	43	17 (39.53)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	16.00 (0.72, 354.80)	4.00 (0.66, 24.37)	0.60 (0.10, 1.00)	0.206
Placebo N=74	5	1 (20.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	12 (54.55)	26.40 (3.01, 231.83)	12.55 (1.78, 88.57)	0.50 (0.28, 0.73)	<0.001	0.520
Placebo N=74	23	1 (4.35)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	23 (60.53)	7.89 (2.79, 22.28)	3.72 (1.80, 7.68)	0.44 (0.25, 0.63)	<0.001
Placebo N=74	43	7 (16.28)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	NC	NC	0.60 (0.17, 1.00)	0.167
Placebo N=74	5	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: General disorders and administration site conditions
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	7 (31.82)	1.32 (0.36, 4.82)	1.22 (0.49, 3.06)	0.06 (-0.21, 0.32)	0.749	0.492
Placebo N=74	23	6 (26.09)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: General disorders and administration site conditions
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	21 (55.26)	2.85 (1.14, 7.10)	1.83 (1.07, 3.13)	0.25 (0.04, 0.46)	0.026
Placebo N=74	43	13 (30.23)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: General disorders and administration site conditions
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	16.00 (0.72, 354.80)	4.00 (0.66, 24.37)	0.60 (0.10, 1.00)	0.206
Placebo N=74	5	1 (20.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Investigations
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	16 (72.73)	3.47 (0.99, 12.09)	1.67 (0.98, 2.85)	0.29 (0.02, 0.57)	0.071	0.135
Placebo N=74	23	10 (43.48)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Investigations
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	23 (60.53)	7.89 (2.79, 22.28)	3.72 (1.80, 7.68)	0.44 (0.25, 0.63)	<0.001
Placebo N=74	43	7 (16.28)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Investigations
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	1.00 (0.08, 12.56)	1.00 (0.22, 4.56)	0.00 (-0.61, 0.61)	1.000
Placebo N=74	5	2 (40.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Race: Asian

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	22	14 (63.64)	NC	NC	0.64 (0.44, 0.84)	<0.001	0.340
Placebo N=74	23	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Race: White

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	38	15 (39.47)	13.37 (2.81, 63.70)	8.49 (2.07, 34.74)	0.35 (0.18, 0.52)	<0.001
Placebo N=74	43	2 (4.65)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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Table 24.2.1.3: Patients with AE by SOC and PT, by Race (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Race: Other

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	1.00 (0.05, 22.18)	1.00 (0.08, 11.93)	0.00 (-0.50, 0.50)	1.000
Placebo N=74	5	1 (20.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factor 'Black or African American' was omitted due to low number of patients (<10). Therefore, the overall number of patients in this subgroup analysis differs from the overall number of patients in full analysis set.
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1.3.2.1.4 UE jeglichen Schweregrads – Ethnie

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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Gastrointestinal disorders
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	5 (100.00)	NC	1.50 (0.95, 2.38)	0.33 (0.03, 0.64)	0.258	0.622
Placebo N=74	9	6 (66.67)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Gastrointestinal disorders
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	45 (71.43)	3.56 (1.69, 7.47)	1.73 (1.24, 2.42)	0.30 (0.14, 0.47)	0.001
Placebo N=74	63	26 (41.27)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	4 (80.00)	NC	NC	0.80 (0.45, 1.00)	0.005	1.000
Placebo N=74	9	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	25 (39.68)	3.95 (1.66, 9.40)	2.78 (1.41, 5.47)	0.25 (0.11, 0.40)	0.002
Placebo N=74	63	9 (14.29)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	NC	NC	0.60 (0.17, 1.00)	0.027	1.000
Placebo N=74	9	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	13 (20.63)	2.47 (0.87, 6.98)	2.17 (0.88, 5.34)	0.11 (-0.01, 0.23)	0.134
Placebo N=74	63	6 (9.52)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	5 (100.00)	NC	1.80 (1.00, 3.23)	0.44 (0.12, 0.77)	0.221	0.262
Placebo N=74	9	5 (55.56)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	56 (88.89)	16.00 (6.22, 41.14)	2.67 (1.86, 3.82)	0.56 (0.42, 0.70)	<0.001
Placebo N=74	63	21 (33.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	NC	NC	0.40 (-0.03, 0.83)	0.110	1.000
Placebo N=74	9	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	37 (58.73)	9.78 (4.00, 23.95)	4.63 (2.34, 9.13)	0.46 (0.31, 0.61)	<0.001
Placebo N=74	63	8 (12.70)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	NC	NC	0.20 (-0.15, 0.55)	0.357	1.000
Placebo N=74	9	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	11 (17.46)	3.12 (0.94, 10.40)	2.75 (0.92, 8.18)	0.11 (-0.00, 0.22)	0.096
Placebo N=74	63	4 (6.35)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Rash
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	NC	NC	0.40 (-0.03, 0.83)	0.110	1.000
Placebo N=74	9	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Rash
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	9 (14.29)	3.33 (0.86, 12.95)	3.00 (0.85, 10.57)	0.10 (-0.01, 0.20)	0.126
Placebo N=74	63	3 (4.76)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: General disorders and administration site conditions
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	3 (60.00)	3.00 (0.31, 28.84)	1.80 (0.56, 5.79)	0.27 (-0.26, 0.80)	0.580	0.905
Placebo N=74	9	3 (33.33)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: General disorders and administration site conditions
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	30 (47.62)	2.27 (1.09, 4.75)	1.67 (1.04, 2.66)	0.19 (0.02, 0.36)	0.043
Placebo N=74	63	18 (28.57)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: General disorders and administration site conditions PT: Oedema peripheral
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	1 (20.00)	NC	NC	0.20 (-0.15, 0.55)	0.357	1.000
Placebo N=74	9	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: General disorders and administration site conditions PT: Oedema peripheral
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	10 (15.87)	11.70 (1.45, 94.40)	10.00 (1.32, 75.82)	0.14 (0.05, 0.24)	0.009
Placebo N=74	63	1 (1.59)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Investigations
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	1.33 (0.14, 12.82)	1.20 (0.29, 4.95)	0.07 (-0.46, 0.60)	1.000	0.396
Placebo N=74	9	3 (33.33)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Investigations
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	41 (65.08)	4.66 (2.19, 9.89)	2.28 (1.48, 3.50)	0.37 (0.20, 0.53)	<0.001
Placebo N=74	63	18 (28.57)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Investigations PT: Aspartate aminotransferase increased
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	63	13 (20.63)	3.84 (1.18, 12.51)	3.25 (1.12, 9.43)	0.14 (0.03, 0.26)	0.035	NC#
Placebo N=74	63	4 (6.35)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Ethnicity: Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	5	2 (40.00)	2.33 (0.22, 25.24)	1.80 (0.35, 9.16)	0.18 (-0.33, 0.69)	0.580	0.056
Placebo N=74	9	2 (22.22)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.4: Patients with AE by SOC and PT, by Ethnicity (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Ethnicity: Not Hispanic or Latino

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	63	29 (46.03)	26.01 (5.85, 115.78)	14.50 (3.61, 58.20)	0.43 (0.30, 0.56)	<0.001
Placebo N=74	63	2 (3.17)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subjects with missing ethnicity are excluded.
Subgroup factors with no events across both treatments have been excluded from the output.
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1.3.2.1.5 UE jeglichen Schweregrads – Geographische Region

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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	8 (88.89)	40.00 (2.01, 794.27)	5.33 (0.88, 32.40)	0.72 (0.36, 1.00)	0.011	0.377
Placebo N=74	6	1 (16.67)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	18 (66.67)	3.40 (1.11, 10.40)	1.80 (1.03, 3.15)	0.30 (0.04, 0.55)	0.056
Placebo N=74	27	10 (37.04)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	13 (72.22)	1.95 (0.51, 7.49)	1.26 (0.79, 2.02)	0.15 (-0.15, 0.45)	0.504
Placebo N=74	21	12 (57.14)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	14 (82.35)	5.70 (1.24, 26.25)	1.83 (1.07, 3.12)	0.37 (0.09, 0.66)	0.040
Placebo N=74	20	9 (45.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	3 (33.33)	NC	NC	0.33 (0.03, 0.64)	0.229	0.680
Placebo N=74	6	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	8 (29.63)	2.42 (0.63, 9.29)	2.00 (0.68, 5.86)	0.15 (-0.07, 0.37)	0.327
Placebo N=74	27	4 (14.81)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	9 (50.00)	6.00 (1.30, 27.77)	3.50 (1.11, 11.00)	0.36 (0.08, 0.63)	0.035
Placebo N=74	21	3 (14.29)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	10 (58.82)	12.86 (2.23, 74.08)	5.88 (1.49, 23.23)	0.49 (0.22, 0.76)	0.004
Placebo N=74	20	2 (10.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	NC	NC	0.44 (0.12, 0.77)	0.103	1.000
Placebo N=74	6	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	10 (37.04)	2.59 (0.74, 9.00)	2.00 (0.79, 5.08)	0.19 (-0.05, 0.42)	0.224
Placebo N=74	27	5 (18.52)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	0 (0.00)	NC	NC	-0.05 (-0.14, 0.04)	1.000
Placebo N=74	21	1 (4.76)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	4 (23.53)	NC	NC	0.24 (0.03, 0.44)	0.036
Placebo N=74	20	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	8 (88.89)	16.00 (1.09, 234.25)	2.67 (0.84, 8.46)	0.56 (0.13, 0.99)	0.089	0.273
Placebo N=74	6	2 (33.33)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	25 (92.59)	29.69 (5.64, 156.19)	3.13 (1.73, 5.64)	0.63 (0.43, 0.83)	<0.001
Placebo N=74	27	8 (29.63)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	17 (94.44)	42.50 (4.58, 394.44)	3.31 (1.67, 6.56)	0.66 (0.44, 0.88)	<0.001
Placebo N=74	21	6 (28.57)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	14 (82.35)	4.67 (1.02, 21.43)	1.65 (1.01, 2.69)	0.32 (0.04, 0.61)	0.082
Placebo N=74	20	10 (50.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	7 (77.78)	17.50 (1.22, 250.36)	4.67 (0.75, 28.89)	0.61 (0.21, 1.00)	0.041	0.837
Placebo N=74	6	1 (16.67)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	18 (66.67)	16.00 (3.78, 67.70)	6.00 (2.00, 18.02)	0.56 (0.34, 0.77)	<0.001
Placebo N=74	27	3 (11.11)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	8 (44.44)	16.00 (1.75, 146.31)	9.33 (1.29, 67.68)	0.40 (0.15, 0.64)	0.006
Placebo N=74	21	1 (4.76)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	9 (52.94)	6.38 (1.35, 30.14)	3.53 (1.13, 10.99)	0.38 (0.10, 0.66)	0.032
Placebo N=74	20	3 (15.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	5 (55.56)	1.25 (0.16, 9.92)	1.11 (0.41, 2.99)	0.06 (-0.46, 0.57)	1.000	0.296
Placebo N=74	6	3 (50.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	19 (70.37)	6.79 (2.06, 22.37)	2.71 (1.37, 5.37)	0.44 (0.21, 0.68)	0.002
Placebo N=74	27	7 (25.93)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	5 (27.78)	0.96 (0.24, 3.90)	0.97 (0.36, 2.66)	-0.01 (-0.29, 0.28)	1.000
Placebo N=74	21	6 (28.57)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	7 (41.18)	2.10 (0.52, 8.51)	1.65 (0.64, 4.25)	0.16 (-0.14, 0.46)	0.482
Placebo N=74	20	5 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	4 (44.44)	0.80 (0.10, 6.35)	0.89 (0.30, 2.63)	-0.06 (-0.57, 0.46)	1.000	0.197
Placebo N=74	6	3 (50.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	15 (55.56)	5.50 (1.60, 18.86)	3.00 (1.27, 7.09)	0.37 (0.13, 0.61)	0.010
Placebo N=74	27	5 (18.52)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	15 (83.33)	5.50 (1.22, 24.81)	1.75 (1.07, 2.87)	0.36 (0.08, 0.63)	0.043
Placebo N=74	21	10 (47.62)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	10 (58.82)	8.10 (1.70, 38.60)	3.92 (1.28, 11.98)	0.44 (0.16, 0.72)	0.008
Placebo N=74	20	3 (15.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: North America

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	9	2 (22.22)	1.43 (0.10, 20.44)	1.33 (0.15, 11.64)	0.06 (-0.35, 0.46)	1.000	0.645
Placebo N=74	6	1 (16.67)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	27	9 (33.33)	13.00 (1.51, 111.78)	9.00 (1.22, 66.23)	0.30 (0.10, 0.49)	0.011
Placebo N=74	27	1 (3.70)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: Asia

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	13 (72.22)	NC	NC	0.72 (0.52, 0.93)	<0.001
Placebo N=74	21	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.5: Patients with AE by SOC and PT, by Geographical Region (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: Rest of the world

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	17	8 (47.06)	8.00 (1.40, 45.76)	4.71 (1.15, 19.24)	0.37 (0.10, 0.64)	0.023
Placebo N=74	20	2 (10.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.2.1.6 UE jeglichen Schweregrads – Lokalisation der Zielläsion

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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	11 (84.62)	5.50 (0.94, 32.21)	1.69 (1.01, 2.84)	0.35 (0.04, 0.65)	0.066	0.584
Placebo N=74	18	9 (50.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	12 (100.00)	NC	2.40 (1.23, 4.69)	0.58 (0.30, 0.86)	0.005
Placebo N=74	12	5 (41.67)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	10 (62.50)	4.44 (0.84, 23.58)	2.29 (0.81, 6.46)	0.35 (-0.00, 0.71)	0.120
Placebo N=74	11	3 (27.27)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	20 (66.67)	2.27 (0.81, 6.34)	1.42 (0.91, 2.22)	0.20 (-0.04, 0.44)	0.133
Placebo N=74	32	15 (46.88)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	5 (38.46)	2.19 (0.45, 10.58)	1.73 (0.57, 5.22)	0.16 (-0.16, 0.49)	0.433	0.709
Placebo N=74	18	4 (22.22)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	9 (75.00)	15.00 (2.02, 111.17)	4.50 (1.22, 16.62)	0.58 (0.26, 0.91)	0.012
Placebo N=74	12	2 (16.67)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	6 (37.50)	NC	NC	0.38 (0.14, 0.61)	0.054
Placebo N=74	11	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	10 (33.33)	4.83 (1.18, 19.80)	3.56 (1.08, 11.69)	0.24 (0.04, 0.44)	0.029
Placebo N=74	32	3 (9.38)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	10 (76.92)	8.67 (1.66, 45.21)	2.77 (1.24, 6.18)	0.49 (0.18, 0.80)	0.011	0.351
Placebo N=74	18	5 (27.78)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	11 (91.67)	33.00 (2.91, 374.31)	3.67 (1.36, 9.91)	0.67 (0.38, 0.96)	0.003
Placebo N=74	12	3 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	14 (87.50)	31.50 (3.74, 265.43)	4.81 (1.36, 17.09)	0.69 (0.41, 0.97)	<0.001
Placebo N=74	11	2 (18.18)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	29 (96.67)	29.00 (3.51, 239.31)	1.93 (1.36, 2.75)	0.47 (0.28, 0.65)	<0.001
Placebo N=74	32	16 (50.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	4 (30.77)	3.56 (0.54, 23.39)	2.77 (0.59, 12.92)	0.20 (-0.09, 0.49)	0.208	0.908
Placebo N=74	18	2 (11.11)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	5 (41.67)	7.86 (0.75, 82.13)	5.00 (0.68, 36.66)	0.33 (0.01, 0.65)	0.155
Placebo N=74	12	1 (8.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	8 (50.00)	NC	NC	0.50 (0.26, 0.74)	0.008
Placebo N=74	11	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	25 (83.33)	27.00 (6.97, 104.54)	5.33 (2.35, 12.12)	0.68 (0.49, 0.86)	<0.001
Placebo N=74	32	5 (15.63)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: General disorders and administration site conditions
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	7 (53.85)	2.33 (0.54, 10.11)	1.62 (0.71, 3.68)	0.21 (-0.14, 0.55)	0.294	0.977
Placebo N=74	18	6 (33.33)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: General disorders and administration site conditions
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	6 (50.00)	3.00 (0.53, 16.90)	2.00 (0.65, 6.20)	0.25 (-0.12, 0.62)	0.400
Placebo N=74	12	3 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: General disorders and administration site conditions
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	9 (56.25)	3.43 (0.66, 17.93)	2.06 (0.72, 5.94)	0.29 (-0.07, 0.65)	0.239
Placebo N=74	11	3 (27.27)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: General disorders and administration site conditions
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	14 (46.67)	2.24 (0.78, 6.41)	1.66 (0.85, 3.25)	0.19 (-0.05, 0.42)	0.189
Placebo N=74	32	9 (28.13)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	4 (30.77)	1.56 (0.31, 7.85)	1.38 (0.42, 4.54)	0.09 (-0.23, 0.40)	0.689	0.203
Placebo N=74	18	4 (22.22)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	9 (75.00)	33.00 (2.91, 374.31)	9.00 (1.34, 60.46)	0.67 (0.38, 0.96)	0.003
Placebo N=74	12	1 (8.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	14 (87.50)	18.67 (2.55, 136.41)	3.21 (1.20, 8.57)	0.60 (0.29, 0.91)	0.003
Placebo N=74	11	3 (27.27)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	17 (56.67)	2.18 (0.79, 6.02)	1.51 (0.88, 2.61)	0.19 (-0.05, 0.44)	0.203
Placebo N=74	32	12 (37.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Target PN Location: Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	13	2 (15.38)	NC	NC	0.15 (-0.04, 0.35)	0.168	1.000
Placebo N=74	18	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Target PN Location: Head/Neck

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	12	4 (33.33)	NC	NC	0.33 (0.07, 0.60)	0.093
Placebo N=74	12	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Target PN Location: Trunk/Extremity

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	16	13 (81.25)	NC	NC	0.81 (0.62, 1.00)	<0.001
Placebo N=74	11	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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Table 24.2.1.6: Patients with AE by SOC and PT, by Target PN Location (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Target PN Location: Trunk

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	30	13 (43.33)	7.39 (1.84, 29.70)	4.62 (1.46, 14.63)	0.34 (0.14, 0.54)	0.003
Placebo N=74	32	3 (9.38)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subject with target PN location 'Other' is excluded.
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1.3.2.1.7 UE jeglichen Schweregrads – Volumen der Zielläsion zu Baseline

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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Gastrointestinal disorders
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	23 (79.31)	6.57 (1.80, 23.98)	2.15 (1.16, 3.99)	0.42 (0.16, 0.69)	0.005	0.602
Placebo N=74	19	7 (36.84)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Gastrointestinal disorders
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	19 (79.17)	4.12 (1.17, 14.50)	1.65 (1.04, 2.60)	0.31 (0.06, 0.57)	0.038
Placebo N=74	25	12 (48.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Gastrointestinal disorders
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	11 (61.11)	2.05 (0.62, 6.76)	1.41 (0.81, 2.45)	0.18 (-0.11, 0.46)	0.371
Placebo N=74	30	13 (43.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	9 (31.03)	8.10 (0.93, 70.37)	5.90 (0.81, 42.85)	0.26 (0.06, 0.45)	0.065	0.347
Placebo N=74	19	1 (5.26)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	13 (54.17)	3.74 (1.11, 12.67)	2.26 (1.03, 4.97)	0.30 (0.04, 0.56)	0.042
Placebo N=74	25	6 (24.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	8 (44.44)	11.20 (2.03, 61.89)	6.67 (1.59, 28.00)	0.38 (0.13, 0.62)	0.003
Placebo N=74	30	2 (6.67)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	28 (96.55)	38.50 (4.30, 344.95)	2.29 (1.35, 3.90)	0.54 (0.31, 0.78)	<0.001	0.433
Placebo N=74	19	8 (42.11)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	21 (87.50)	22.17 (4.86, 101.20)	3.65 (1.79, 7.44)	0.64 (0.42, 0.85)	<0.001
Placebo N=74	25	6 (24.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	15 (83.33)	7.50 (1.78, 31.62)	2.08 (1.28, 3.38)	0.43 (0.19, 0.68)	0.006
Placebo N=74	30	12 (40.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	22 (75.86)	11.79 (2.93, 47.45)	3.60 (1.47, 8.82)	0.55 (0.31, 0.79)	<0.001	0.568
Placebo N=74	19	4 (21.05)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	11 (45.83)	20.31 (2.35, 175.30)	11.46 (1.60, 82.08)	0.42 (0.20, 0.63)	<0.001
Placebo N=74	25	1 (4.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	9 (50.00)	9.00 (1.99, 40.69)	5.00 (1.55, 16.09)	0.40 (0.15, 0.65)	0.004
Placebo N=74	30	3 (10.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: General disorders and administration site conditions
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	15 (51.72)	4.02 (1.07, 15.07)	2.46 (0.96, 6.28)	0.31 (0.05, 0.56)	0.041	0.201
Placebo N=74	19	4 (21.05)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: General disorders and administration site conditions
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	13 (54.17)	4.73 (1.33, 16.78)	2.71 (1.14, 6.44)	0.34 (0.09, 0.60)	0.019
Placebo N=74	25	5 (20.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: General disorders and administration site conditions
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	8 (44.44)	1.20 (0.37, 3.91)	1.11 (0.56, 2.19)	0.04 (-0.24, 0.33)	0.772
Placebo N=74	30	12 (40.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Investigations
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	14 (48.28)	2.61 (0.75, 9.16)	1.83 (0.79, 4.26)	0.22 (-0.05, 0.49)	0.147	0.393
Placebo N=74	19	5 (26.32)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Investigations
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	16 (66.67)	3.56 (1.09, 11.55)	1.85 (1.02, 3.36)	0.31 (0.04, 0.57)	0.046
Placebo N=74	25	9 (36.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Investigations
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	14 (77.78)	11.50 (2.85, 46.48)	3.33 (1.67, 6.67)	0.54 (0.30, 0.79)	<0.001
Placebo N=74	30	7 (23.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Baseline Target PN Volume: 0 - < 54

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	29	9 (31.03)	3.83 (0.73, 20.18)	2.95 (0.71, 12.18)	0.21 (-0.01, 0.42)	0.161	0.272
Placebo N=74	19	2 (10.53)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Baseline Target PN Volume: 54 - < 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	24	13 (54.17)	28.36 (3.29, 244.84)	13.54 (1.92, 95.69)	0.50 (0.29, 0.72)	<0.001
Placebo N=74	25	1 (4.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.7: Patients with AE by SOC and PT, by Baseline Target PN Volume (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Baseline Target PN Volume: >= 333

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	18	10 (55.56)	36.25 (4.02, 327.03)	16.67 (2.32, 119.61)	0.52 (0.28, 0.76)	<0.001
Placebo N=74	30	1 (3.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.2.1.8 UE jeglichen Schweregrads – Durchschnittlicher PAINS-pNF-Wert für chronische Schmerzen der Zielläsion zu Baseline

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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Gastrointestinal disorders
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	15 (71.43)	3.33 (0.93, 12.01)	1.67 (0.95, 2.93)	0.29 (-0.00, 0.57)	0.118	0.883
Placebo N=74	21	9 (42.86)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Gastrointestinal disorders
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	38 (76.00)	4.13 (1.77, 9.63)	1.75 (1.24, 2.47)	0.33 (0.15, 0.50)	0.001
Placebo N=74	53	23 (43.40)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	8 (38.10)	12.31 (1.37, 110.30)	8.00 (1.09, 58.46)	0.33 (0.11, 0.56)	0.020	0.349
Placebo N=74	21	1 (4.76)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	22 (44.00)	4.42 (1.73, 11.28)	2.92 (1.43, 5.93)	0.29 (0.12, 0.46)	0.002
Placebo N=74	53	8 (15.09)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	6 (28.57)	3.80 (0.67, 21.60)	3.00 (0.68, 13.20)	0.19 (-0.04, 0.42)	0.238	0.950
Placebo N=74	21	2 (9.52)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	12 (24.00)	3.87 (1.16, 12.95)	3.18 (1.10, 9.21)	0.16 (0.03, 0.30)	0.029
Placebo N=74	53	4 (7.55)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	16 (76.19)	10.24 (2.47, 42.37)	3.20 (1.44, 7.13)	0.52 (0.27, 0.78)	0.002	0.531
Placebo N=74	21	5 (23.81)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	48 (96.00)	36.57 (8.02, 166.85)	2.42 (1.73, 3.39)	0.56 (0.42, 0.71)	<0.001
Placebo N=74	53	21 (39.62)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	11 (52.38)	10.45 (1.93, 56.64)	5.50 (1.38, 21.86)	0.43 (0.18, 0.68)	0.006	0.996
Placebo N=74	21	2 (9.52)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	31 (62.00)	12.78 (4.59, 35.58)	5.48 (2.50, 12.00)	0.51 (0.35, 0.67)	<0.001
Placebo N=74	53	6 (11.32)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	3 (14.29)	3.33 (0.32, 34.99)	3.00 (0.34, 26.56)	0.10 (-0.08, 0.27)	0.606	0.898
Placebo N=74	21	1 (4.76)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	10 (20.00)	4.17 (1.07, 16.16)	3.53 (1.03, 12.10)	0.14 (0.02, 0.27)	0.038
Placebo N=74	53	3 (5.66)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: General disorders and administration site conditions
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	8 (38.10)	1.54 (0.42, 5.61)	1.33 (0.56, 3.18)	0.10 (-0.19, 0.38)	0.744	0.439
Placebo N=74	21	6 (28.57)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: General disorders and administration site conditions
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	28 (56.00)	3.22 (1.42, 7.31)	1.98 (1.21, 3.24)	0.28 (0.09, 0.46)	0.005
Placebo N=74	53	15 (28.30)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Investigations
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	12 (57.14)	1.78 (0.52, 6.04)	1.33 (0.72, 2.47)	0.14 (-0.16, 0.44)	0.538	0.072
Placebo N=74	21	9 (42.86)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Investigations
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	32 (64.00)	6.07 (2.56, 14.42)	2.83 (1.65, 4.85)	0.41 (0.24, 0.59)	<0.001
Placebo N=74	53	12 (22.64)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Average Baseline PAINS-pNF Chronic Target PN Pain Score: < 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	21	6 (28.57)	8.00 (0.87, 73.68)	6.00 (0.79, 45.63)	0.24 (0.02, 0.45)	0.093	0.719
Placebo N=74	21	1 (4.76)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1.8: Patients with AE by SOC and PT, by Average Baseline PAINS-pNF Chronic Target PN Pain Score (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Average Baseline PAINS-pNF Chronic Target PN Pain Score: >= 3

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	50	26 (52.00)	18.06 (4.97, 65.62)	9.19 (2.96, 28.46)	0.46 (0.31, 0.62)	<0.001
Placebo N=74	53	3 (5.66)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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1.3.2.1.9 UE jeglichen Schweregrads – Geographische Region (Stratifikation)

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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	8 (72.73)	1.19 (0.20, 6.99)	1.05 (0.63, 1.75)	0.03 (-0.33, 0.40)	1.000	0.205
Placebo N=74	13	9 (69.23)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	5 (71.43)	4.17 (0.47, 36.74)	1.90 (0.69, 5.23)	0.34 (-0.13, 0.81)	0.315
Placebo N=74	8	3 (37.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	19 (61.29)	3.17 (1.11, 9.03)	1.84 (1.03, 3.28)	0.28 (0.04, 0.52)	0.041
Placebo N=74	30	10 (33.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	21 (95.45)	27.30 (3.12, 238.83)	2.20 (1.37, 3.53)	0.52 (0.30, 0.74)	<0.001
Placebo N=74	23	10 (43.48)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	7 (63.64)	21.00 (1.94, 227.20)	8.27 (1.19, 57.30)	0.56 (0.24, 0.88)	0.008	0.229
Placebo N=74	13	1 (7.69)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	2 (28.57)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.04 (-0.41, 0.49)	1.000
Placebo N=74	8	2 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	8 (25.81)	2.26 (0.60, 8.50)	1.94 (0.65, 5.76)	0.12 (-0.07, 0.32)	0.335
Placebo N=74	30	4 (13.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	13 (59.09)	15.17 (2.82, 81.46)	6.80 (1.73, 26.72)	0.50 (0.27, 0.74)	<0.001
Placebo N=74	23	2 (8.70)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	0 (0.00)	NC	NC	-0.08 (-0.22, 0.07)	1.000	1.000
Placebo N=74	13	1 (7.69)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	11 (35.48)	2.75 (0.82, 9.22)	2.13 (0.84, 5.40)	0.19 (-0.03, 0.40)	0.146
Placebo N=74	30	5 (16.67)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	7 (31.82)	NC	NC	0.32 (0.12, 0.51)	0.004
Placebo N=74	23	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	10 (90.91)	16.00 (1.54, 166.05)	2.36 (1.16, 4.82)	0.52 (0.21, 0.84)	0.013	0.488
Placebo N=74	13	5 (38.46)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	7 (100.00)	NC	8.00 (1.28, 50.04)	0.88 (0.65, 1.00)	0.001
Placebo N=74	8	1 (12.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	28 (90.32)	18.67 (4.55, 76.62)	2.71 (1.61, 4.55)	0.57 (0.37, 0.77)	<0.001
Placebo N=74	30	10 (33.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	19 (86.36)	8.23 (1.89, 35.83)	1.99 (1.21, 3.26)	0.43 (0.18, 0.68)	0.005
Placebo N=74	23	10 (43.48)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	1 (9.09)	NC	NC	0.09 (-0.08, 0.26)	0.458	0.823
Placebo N=74	13	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	7 (100.00)	NC	8.00 (1.28, 50.04)	0.88 (0.65, 1.00)	0.001
Placebo N=74	8	1 (12.50)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	20 (64.52)	9.09 (2.71, 30.48)	3.87 (1.67, 8.98)	0.48 (0.26, 0.69)	<0.001
Placebo N=74	30	5 (16.67)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	14 (63.64)	18.38 (3.39, 99.65)	7.32 (1.88, 28.55)	0.55 (0.32, 0.78)	<0.001
Placebo N=74	23	2 (8.70)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	3 (27.27)	0.84 (0.14, 4.97)	0.89 (0.25, 3.14)	-0.03 (-0.40, 0.33)	1.000	0.346
Placebo N=74	13	4 (30.77)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	2 (28.57)	1.20 (0.12, 11.87)	1.14 (0.21, 6.11)	0.04 (-0.41, 0.49)	1.000
Placebo N=74	8	2 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	20 (64.52)	5.97 (1.95, 18.33)	2.76 (1.37, 5.56)	0.41 (0.19, 0.64)	0.002
Placebo N=74	30	7 (23.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: General disorders and administration site conditions
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	11 (50.00)	1.88 (0.57, 6.21)	1.44 (0.71, 2.89)	0.15 (-0.13, 0.44)	0.373
Placebo N=74	23	8 (34.78)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	10 (90.91)	6.25 (0.60, 64.86)	1.48 (0.92, 2.36)	0.29 (-0.02, 0.61)	0.166	0.330
Placebo N=74	13	8 (61.54)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	5 (71.43)	7.50 (0.76, 74.16)	2.86 (0.79, 10.36)	0.46 (0.01, 0.91)	0.132
Placebo N=74	8	2 (25.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	18 (58.06)	6.92 (2.09, 22.90)	3.48 (1.48, 8.19)	0.41 (0.19, 0.63)	0.001
Placebo N=74	30	5 (16.67)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	11 (50.00)	2.83 (0.81, 9.90)	1.92 (0.86, 4.29)	0.24 (-0.04, 0.51)	0.130
Placebo N=74	23	6 (26.09)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: China

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]	Interaction p-value [b]
Selumetinib 25 mg/m2 BID N=71	11	8 (72.73)	NC	NC	0.73 (0.46, 0.99)	<0.001	0.732
Placebo N=74	13	0 (0.00)					

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
[b] p-value for interaction between treatment and subgroup factors using Cochran's Q test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: Japan

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	7	5 (71.43)	NC	NC	0.71 (0.38, 1.00)	0.007
Placebo N=74	8	0 (0.00)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: Europe

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	31	11 (35.48)	15.95 (1.91, 133.53)	10.65 (1.46, 77.46)	0.32 (0.14, 0.50)	0.003
Placebo N=74	30	1 (3.33)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1.9: Patients with AE by SOC and PT, by Geographical Region (Stratification Factor) (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased
Geographical Region: Rest of World

Treatment group	n	Subjects with event Number (%)	OR 95% CI	RR 95% CI	RD 95% CI	p-value [a]
Selumetinib 25 mg/m2 BID N=71	22	8 (36.36)	3.81 (0.86, 16.94)	2.79 (0.85, 9.18)	0.23 (-0.01, 0.48)	0.091
Placebo N=74	23	3 (13.04)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomised Period Safety Analysis Set; n = Number of subjects in respective subgroup factor
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Subgroup factors with no events across both treatments have been excluded from the output.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:33

2 Ergänzende Analysen

2.1 Rücklaufquoten

2.1.1 PAINS-pNF

2.1.1.1 PAINS-pNF, chronischer Schmerz – FAS

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.17.1: eDiary compliance rate for PAINS-pNF chronic target PN pain over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1542 (77.6)	2072	1532 (73.9)
Cycle 1	1988	1922 (96.7)	2072	2036 (98.3)
Cycle 2	1988	1814 (91.2)	2072	2023 (97.6)
Cycle 3	1988	1776 (89.3)	2072	1963 (94.7)
Cycle 4	1988	1722 (86.6)	2072	1954 (94.3)
Cycle 5	1988	1712 (86.1)	2072	1889 (91.2)
Cycle 6	1988	1660 (83.5)	2072	1892 (91.3)
Cycle 7	1988	1661 (83.6)	2072	1858 (89.7)
Cycle 8	1988	1626 (81.8)	2072	1837 (88.7)
Cycle 9	1988	1596 (80.3)	2072	1774 (85.6)
Cycle 10	1988	1565 (78.7)	2072	1768 (85.3)
Cycle 11	1988	1527 (76.8)	2072	1734 (83.7)
Cycle 12	1988	1482 (74.5)	2072	1698 (81.9)

[a] Number of expected daily diary entries for all patients in full analysis set.
[b] A diary entry is considered completed if a daily chronic target PAINS-pNF pain score was recorded.
N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pnpnf.sas Executed: 07FEB2025:12:02:34

2.1.1.2 PAINS-pNF, chronischer Schmerz – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.18.1: eDiary compliance rate for PAINS-
pNF chronic target PN pain over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1542 (77.6)	2072	1532 (73.9)
Cycle 1	1942	1922 (99.0)	2072	2036 (98.3)
Cycle 2	1881	1814 (96.4)	2070	2023 (97.7)
Cycle 3	1835	1776 (96.8)	2044	1963 (96.0)
Cycle 4	1820	1722 (94.6)	2005	1954 (97.5)
Cycle 5	1820	1712 (94.1)	1960	1889 (96.4)
Cycle 6	1820	1660 (91.2)	1954	1892 (96.8)
Cycle 7	1809	1661 (91.8)	1932	1858 (96.2)
Cycle 8	1776	1626 (91.6)	1925	1837 (95.4)
Cycle 9	1712	1596 (93.2)	1904	1774 (93.2)
Cycle 10	1706	1565 (91.7)	1879	1768 (94.1)
Cycle 11	1659	1527 (92.0)	1870	1734 (92.7)
Cycle 12	1624	1482 (91.3)	1848	1698 (91.9)

[a] Number of expected daily diary entries while patient is on treatment.
[b] A diary entry is considered completed if a daily chronic target PAINS-pNF pain score was recorded.
N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pnpnf.sas Executed: 07FEB2025:12:02:36

2.1.1.3 PAINS-pNF, Schmerzspitze – FAS

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.8.1: eDiary compliance rate for PAINS-pNF spike target PN pain over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1542 (77.6)	2072	1532 (73.9)
Cycle 1	1988	1922 (96.7)	2072	2036 (98.3)
Cycle 2	1988	1814 (91.2)	2072	2023 (97.6)
Cycle 3	1988	1776 (89.3)	2072	1963 (94.7)
Cycle 4	1988	1722 (86.6)	2072	1954 (94.3)
Cycle 5	1988	1712 (86.1)	2072	1889 (91.2)
Cycle 6	1988	1660 (83.5)	2072	1892 (91.3)
Cycle 7	1988	1661 (83.6)	2072	1858 (89.7)
Cycle 8	1988	1626 (81.8)	2072	1837 (88.7)
Cycle 9	1988	1596 (80.3)	2072	1774 (85.6)
Cycle 10	1988	1565 (78.7)	2072	1768 (85.3)
Cycle 11	1988	1527 (76.8)	2072	1734 (83.7)
Cycle 12	1988	1482 (74.5)	2072	1698 (81.9)

[a] Number of expected daily diary entries for all patients in full analysis set.
[b] A diary entry is considered completed if a daily spike target PAINS-pNF pain score was recorded.
N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pnpnf.sas Executed: 07FEB2025:12:02:20

2.1.1.4 PAINS-pNF, Schmerzspitze – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.9.1: eDiary compliance rate for PAINS-
pNF spike target PN pain over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1542 (77.6)	2072	1532 (73.9)
Cycle 1	1942	1922 (99.0)	2072	2036 (98.3)
Cycle 2	1881	1814 (96.4)	2070	2023 (97.7)
Cycle 3	1835	1776 (96.8)	2044	1963 (96.0)
Cycle 4	1820	1722 (94.6)	2005	1954 (97.5)
Cycle 5	1820	1712 (94.1)	1960	1889 (96.4)
Cycle 6	1820	1660 (91.2)	1954	1892 (96.8)
Cycle 7	1809	1661 (91.8)	1932	1858 (96.2)
Cycle 8	1776	1626 (91.6)	1925	1837 (95.4)
Cycle 9	1712	1596 (93.2)	1904	1774 (93.2)
Cycle 10	1706	1565 (91.7)	1879	1768 (94.1)
Cycle 11	1659	1527 (92.0)	1870	1734 (92.7)
Cycle 12	1624	1482 (91.3)	1848	1698 (91.9)

[a] Number of expected daily diary entries while patient is on treatment.
[b] A diary entry is considered completed if a daily spike target PAINS-pNF pain score was recorded.
N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pnpnf.sas Executed: 07FEB2025:12:02:27

2.1.2 PGIC

2.1.2.1 PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum), chronischer Schmerz – FAS

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PSC_U Data Cut-Off 2024-08-05
Table 17.14.1: Instrument completion rate for PGIC with chronic pain responses since last visit to the study site over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Timepoint	PGIC assessment completed [a] n (%)	PGIC assessment completed [a] n (%)
Cycle 1, Day 28	67 (94.37)	74 (100)
Cycle 2, Day 28	65 (91.55)	73 (98.65)
Cycle 4, Day 28	64 (90.14)	68 (91.89)
Cycle 6, Day 28	64 (90.14)	67 (90.54)
Cycle 8, Day 28	58 (81.69)	64 (86.49)
Cycle 10, Day 28	58 (81.69)	60 (81.08)
Cycle 12, Day 28	57 (80.28)	58 (78.38)

[a] Completion rate is calculated among subjects in Full analysis set.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:26

2.1.2.2 PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum), chronischer Schmerz – FAS – bezogen auf alle Patienten unter Behandlung

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PSC_U Data Cut-Off 2024-08-05
Table 17.15.1: Instrument completion rate for PGIC with chronic pain responses since last visit to the study site over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	PGIC assessment expected n	PGIC assessment completed [a] n (%)	PGIC assessment expected n	PGIC assessment completed [a] n (%)
Cycle 1, Day 28	71	67 (94.37)	74	74 (100)
Cycle 2, Day 28	67	65 (97.01)	74	73 (98.65)
Cycle 4, Day 28	65	64 (98.46)	73	68 (93.15)
Cycle 6, Day 28	65	64 (98.46)	70	67 (95.71)
Cycle 8, Day 28	64	58 (90.63)	69	64 (92.75)
Cycle 10, Day 28	61	58 (95.08)	68	60 (88.24)
Cycle 12, Day 28	58	57 (98.28)	66	58 (87.88)

[a] Completion rate is calculated among subjects with a PGIC assessment expected.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:26

2.1.2.3 PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum), Schmerzspitze – FAS

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PSC_U Data Cut-Off 2024-08-05
Table 17.29.1: Instrument completion rate for PGIC with spike of pain responses since last visit to the study site over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
	PGIC assessment completed [a]	PGIC assessment completed [a]
Timepoint	n (%)	n (%)
Cycle 1, Day 28	67 (94.37)	74 (100)
Cycle 2, Day 28	65 (91.55)	73 (98.65)
Cycle 4, Day 28	64 (90.14)	68 (91.89)
Cycle 6, Day 28	64 (90.14)	67 (90.54)
Cycle 8, Day 28	58 (81.69)	64 (86.49)
Cycle 10, Day 28	58 (81.69)	60 (81.08)
Cycle 12, Day 28	57 (80.28)	58 (78.38)

[a] Completion rate is calculated among subjects in Full analysis set.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:27

2.1.2.4 PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum), Schmerzspitze – FAS – bezogen auf alle Patienten unter Behandlung

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PSC_U Data Cut-Off 2024-08-05
Table 17.30.1: Instrument completion rate for PGIC with spike of pain responses since last visit to the study site over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	PGIC assessment expected n	PGIC assessment completed [a] n (%)	PGIC assessment expected n	PGIC assessment completed [a] n (%)
Cycle 1, Day 28	71	67 (94.37)	74	74 (100)
Cycle 2, Day 28	67	65 (97.01)	74	73 (98.65)
Cycle 4, Day 28	65	64 (98.46)	73	68 (93.15)
Cycle 6, Day 28	65	64 (98.46)	70	67 (95.71)
Cycle 8, Day 28	64	58 (90.63)	69	64 (92.75)
Cycle 10, Day 28	61	58 (95.08)	68	60 (88.24)
Cycle 12, Day 28	58	57 (98.28)	66	58 (87.88)

[a] Completion rate is calculated among subjects with a PGIC assessment expected.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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2.1.2.5 PGIC 2 (Schmerzen seit Beginn der Studienmedikation), chronischer Schmerz – FAS

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PSC_U Data Cut-Off 2024-08-05
Table 17.44.1: Instrument completion rate for PGIC with chronic pain responses since starting the study medication over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
	PGIC assessment completed [a]	PGIC assessment completed [a]
Timepoint	n (%)	n (%)
Cycle 12, Day 28	57 (80.28)	58 (78.38)

[a] Completion rate is calculated among subjects in Full analysis set.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 26SEP2025 13:06:36

2.1.2.6 PGIC 2 (Schmerzen seit Beginn der Studienmedikation), chronischer Schmerz – FAS – bezogen auf alle Patienten unter Behandlung

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PSC_U Data Cut-Off 2024-08-05
Table 17.45.1: Instrument completion rate for PGIC with chronic pain responses since starting the study medication over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	PGIC assessment expected n	PGIC assessment completed [a] n (%)	PGIC assessment expected n	PGIC assessment completed [a] n (%)
Cycle 12, Day 28	58	57 (98.28)	66	58 (87.88)

[a] Completion rate is calculated among subjects with a PGIC assessment expected.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 26SEP2025 13:06:37

2.1.2.7 PGIC 2 (Schmerzen seit Beginn der Studienmedikation), Schmerzspitze – FAS

Protocol Number: D134BC00001 Phase III Page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 17.59.1: Instrument completion rate for PGIC with spike of pain responses since starting the study medication over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
	PGIC assessment completed [a]	PGIC assessment completed [a]
Timepoint	n (%)	n (%)
Cycle 12, Day 28	57 (80.28)	58 (78.38)

[a] Completion rate is calculated among subjects in Full analysis set.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 26SEP2025 13:06:38

2.1.2.8 PGIC 2 (Schmerzen seit Beginn der Studienmedikation), Schmerzspitze – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III Page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 17.60.1: Instrument completion rate for PGIC with spike of pain responses since starting the study medication over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	PGIC assessment expected n	PGIC assessment completed [a] n (%)	PGIC assessment expected n	PGIC assessment completed [a] n (%)
Cycle 12, Day 28	58	57 (98.28)	66	58 (87.88)

[a] Completion rate is calculated among subjects with a PGIC assessment expected.
PGIC = Patient Global Impression of Change.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 26SEP2025 13:06:38

2.1.3 PGIS

2.1.3.1 PGIS, chronischer Schmerz – FAS

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 18.8.1: Instrument completion rate for PGIS with chronic pain responses over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
	PGIS assessment completed [a]	PGIS assessment completed [a]
Timepoint	n (%)	n (%)
Baseline	70 (98.59)	72 (97.30)
Cycle 1, Day 28	67 (94.37)	74 (100)
Cycle 2, Day 28	65 (91.55)	73 (98.65)
Cycle 4, Day 28	64 (90.14)	68 (91.89)
Cycle 6, Day 28	64 (90.14)	67 (90.54)
Cycle 8, Day 28	58 (81.69)	64 (86.49)
Cycle 10, Day 28	58 (81.69)	60 (81.08)
Cycle 12, Day 28	57 (80.28)	58 (78.38)

[a] Completion rate is calculated among subjects in Full analysis set.
PGIS = Patient Global Impression of Severity.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:23

2.1.3.2 PGIS, chronischer Schmerz – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 18.9.1: Instrument completion rate for PGIS with chronic pain responses over the randomised period (Full Analysis Set) - among subjects expected to have an a ssessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	PGIS assessment expected n	PGIS assessment completed [a] n (%)	PGIS assessment expected n	PGIS assessment completed [a] n (%)
Baseline	71	70 (98.59)	74	72 (97.30)
Cycle 1, Day 28	71	67 (94.37)	74	74 (100)
Cycle 2, Day 28	67	65 (97.01)	74	73 (98.65)
Cycle 4, Day 28	65	64 (98.46)	73	68 (93.15)
Cycle 6, Day 28	65	64 (98.46)	70	67 (95.71)
Cycle 8, Day 28	64	58 (90.63)	69	64 (92.75)
Cycle 10, Day 28	61	58 (95.08)	68	60 (88.24)
Cycle 12, Day 28	58	57 (98.28)	66	58 (87.88)

[a] Completion rate is calculated among subjects with a PGIS assessment expected.
PGIS = Patient Global Impression of Severity.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:24

2.1.3.3 PGIS, Schmerzspitze – FAS

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 18.17.1: Instrument completion rate for PGIS with spike of pain responses over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
	PGIS assessment completed [a]	PGIS assessment completed [a]
Timepoint	n (%)	n (%)
Baseline	70 (98.59)	72 (97.30)
Cycle 1, Day 28	67 (94.37)	74 (100)
Cycle 2, Day 28	65 (91.55)	73 (98.65)
Cycle 4, Day 28	64 (90.14)	68 (91.89)
Cycle 6, Day 28	64 (90.14)	67 (90.54)
Cycle 8, Day 28	58 (81.69)	64 (86.49)
Cycle 10, Day 28	58 (81.69)	60 (81.08)
Cycle 12, Day 28	57 (80.28)	58 (78.38)

[a] Completion rate is calculated among subjects in Full analysis set.
PGIS = Patient Global Impression of Severity.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:24

2.1.3.4 PGIS, Schmerzspitze – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 18.18.1: Instrument completion rate for PGIS with spike of pain responses over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	PGIS assessment expected n	PGIS assessment completed [a] n (%)	PGIS assessment expected n	PGIS assessment completed [a] n (%)
Baseline	71	70 (98.59)	74	72 (97.30)
Cycle 1, Day 28	71	67 (94.37)	74	74 (100)
Cycle 2, Day 28	67	65 (97.01)	74	73 (98.65)
Cycle 4, Day 28	65	64 (98.46)	73	68 (93.15)
Cycle 6, Day 28	65	64 (98.46)	70	67 (95.71)
Cycle 8, Day 28	64	58 (90.63)	69	64 (92.75)
Cycle 10, Day 28	61	58 (95.08)	68	60 (88.24)
Cycle 12, Day 28	58	57 (98.28)	66	58 (87.88)

[a] Completion rate is calculated among subjects with a PGIS assessment expected.
PGIS = Patient Global Impression of Severity.
n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_pgi.sas Executed: 11FEB2025 18:52:25

2.1.4 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch

2.1.4.1 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch – FAS

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.26.1: eDiary compliance rate for chronic PN pain medication over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1498 (75.4)	2072	1449 (69.9)
Cycle 1	1988	1869 (94.0)	2072	1932 (93.2)
Cycle 2	1988	1778 (89.4)	2072	1931 (93.2)
Cycle 3	1988	1733 (87.2)	2072	1871 (90.3)
Cycle 4	1988	1682 (84.6)	2072	1877 (90.6)
Cycle 5	1988	1664 (83.7)	2072	1828 (88.2)
Cycle 6	1988	1623 (81.6)	2072	1803 (87.0)
Cycle 7	1988	1619 (81.4)	2072	1773 (85.6)
Cycle 8	1988	1597 (80.3)	2072	1747 (84.3)
Cycle 9	1988	1549 (77.9)	2072	1694 (81.8)
Cycle 10	1988	1526 (76.8)	2072	1691 (81.6)
Cycle 11	1988	1483 (74.6)	2072	1648 (79.5)
Cycle 12	1988	1444 (72.6)	2072	1625 (78.4)

[a] Number of expected daily diary entries for all patients in full analysis set.
[b] A diary entry is considered completed if question 'Did you take any medication for your tumour pain from the time you went to bed last night until now (including overnight)?' was answered and the items after it are answered if applicable.
N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_painmed_ediary.sas Executed: 06AUG2025:18:06:54

2.1.4.2 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.27.1: eDiary compliance rate for chronic PN pain medication over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1498 (75.4)	2072	1449 (69.9)
Cycle 1	1942	1869 (96.2)	2072	1932 (93.2)
Cycle 2	1881	1778 (94.5)	2070	1931 (93.3)
Cycle 3	1835	1733 (94.4)	2044	1871 (91.5)
Cycle 4	1820	1682 (92.4)	2005	1877 (93.6)
Cycle 5	1820	1664 (91.4)	1960	1828 (93.3)
Cycle 6	1820	1623 (89.2)	1954	1803 (92.3)
Cycle 7	1809	1619 (89.5)	1932	1773 (91.8)
Cycle 8	1776	1597 (89.9)	1925	1747 (90.8)
Cycle 9	1712	1549 (90.5)	1904	1694 (89.0)
Cycle 10	1706	1526 (89.4)	1879	1691 (90.0)
Cycle 11	1659	1483 (89.4)	1870	1648 (88.1)
Cycle 12	1624	1444 (88.9)	1848	1625 (87.9)

[a] Number of expected daily diary entries while patient is on treatment.
[b] A diary entry is considered completed if question 'Did you take any medication for your tumour pain from the time you went to bed last night until now (including overnight)?' was answered and the items after it are answered if applicable.
N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_cmpl_painmed_ediary.sas Executed: 06AUG2025:18:06:55

2.1.5 PII-pNF

2.1.5.1 PII-pNF – FAS

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 15.8.1: Instrument completion rate for PII-PNF over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	All questions completed [a] n (%)	At least one question completed [a] n (%)	All questions completed [a] n (%)	At least one question completed [a] n (%)
Baseline	47 (66.2)	70 (98.6)	50 (67.6)	72 (97.3)
Cycle 1, Day 28	45 (63.4)	67 (94.4)	54 (73.0)	74 (100)
Cycle 2, Day 28	44 (62.0)	65 (91.5)	54 (73.0)	73 (98.6)
Cycle 4, Day 28	45 (63.4)	64 (90.1)	49 (66.2)	68 (91.9)
Cycle 6, Day 28	43 (60.6)	64 (90.1)	48 (64.9)	67 (90.5)
Cycle 8, Day 28	44 (62.0)	58 (81.7)	44 (59.5)	64 (86.5)
Cycle 10, Day 28	37 (52.1)	59 (83.1)	44 (59.5)	63 (85.1)
Cycle 12, Day 28	40 (56.3)	58 (81.7)	43 (58.1)	61 (82.4)

[a] Completion rate is calculated among subjects in Full analysis set. Subjects are expected to complete PROs while on treatment.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PII-pNF Pain interference index – plexiform neurofibroma.
Program: t_cmpl_piipnf.sas Executed: 24FEB2025 16:35:41

2.1.5.2 PII-pNF – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 15.9.1: Instrument completion rate for PII-PNF over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)			Placebo (N=74)		
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)
Baseline	71	47 (66.2)	70 (98.6)	74	50 (67.6)	72 (97.3)
Cycle 1, Day 28	71	45 (63.4)	67 (94.4)	74	54 (73.0)	74 (100)
Cycle 2, Day 28	67	44 (65.7)	65 (97.0)	74	54 (73.0)	73 (98.6)
Cycle 4, Day 28	65	45 (69.2)	64 (98.5)	73	49 (67.1)	68 (93.2)
Cycle 6, Day 28	65	43 (66.2)	64 (98.5)	70	48 (68.6)	67 (95.7)
Cycle 8, Day 28	64	44 (68.8)	58 (90.6)	69	44 (63.8)	64 (92.8)
Cycle 10, Day 28	61	37 (60.7)	59 (96.7)	68	44 (64.7)	63 (92.6)
Cycle 12, Day 28	58	40 (69.0)	58 (100)	66	43 (65.2)	61 (92.4)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100 % when
a subject continues to complete after discontinuation.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PII-pNF Pain interference index – plexiform neurofibroma.
Program: t_cmpl_piipnf.sas Executed: 24FEB2025 16:35:44

2.1.6 EQ-5D VAS

2.1.6.1 EQ-5D VAS – FAS

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 13.8.1: Instrument completion rate for EQ-VAS over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Timepoint	EQ-VAS Completed [a] n (%)	EQ-VAS Completed [a] n (%)
Baseline	70 (98.6)	72 (97.3)
Cycle 2, Day 28	64 (90.1)	73 (98.6)
Cycle 4, Day 28	64 (90.1)	68 (91.9)
Cycle 8, Day 28	59 (83.1)	65 (87.8)
Cycle 12, Day 28	58 (81.7)	61 (82.4)

[a] Completion rate is calculated among subjects in Full analysis set. Subjects are expected to complete EQ-VAS while on treatment.
Full Analysis Set consists of subjects randomised to study intervention in the study.
EQ-VAS EuroQol visual analogue scale.
Program: t_cmpl_eqvas.sas Executed: 01OCT2025 17:13:05

2.1.6.2 EQ-5D VAS – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 13.9.1: Instrument completion rate for EQ-VAS over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	EQ-VAS Expected n	EQ-VAS Completed [a] n (%)	EQ-VAS Expected n	EQ-VAS Completed [a] n (%)
Baseline	71	70 (98.6)	74	72 (97.3)
Cycle 2, Day 28	71	64 (90.1)	74	73 (98.6)
Cycle 4, Day 28	65	64 (98.5)	73	68 (93.2)
Cycle 8, Day 28	65	59 (90.8)	69	65 (94.2)
Cycle 12, Day 28	60	58 (96.7)	67	61 (91.0)

[a] Completion rate is calculated among subjects with a EQ-VAS expected. Subjects are expected to complete EQ-VAS while on treatment. Rate greater than 100% when a subject continues to complete after discontinuation.
Full Analysis Set consists of subjects randomised to study intervention in the study.
EQ-VAS EuroQol visual analogue scale.
Program: t_cmpl_eqvas.sas Executed: 01OCT2025 17:13:06

2.1.7 PROMIS

2.1.7.1 PROMIS – FAS

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 16.8.1: Instrument completion rate for PROMIS over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo (N=74)	
Timepoint	All questions completed [a] n (%)	At least one question completed [a] n (%)	All questions completed [a] n (%)	At least one question completed [a] n (%)
Baseline	70 (98.6)	70 (98.6)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	64 (90.1)	64 (90.1)	73 (98.6)	73 (98.6)
Cycle 4, Day 28	64 (90.1)	64 (90.1)	68 (91.9)	68 (91.9)
Cycle 8, Day 28	59 (83.1)	59 (83.1)	65 (87.8)	65 (87.8)
Cycle 12, Day 28	58 (81.7)	58 (81.7)	61 (82.4)	61 (82.4)

[a] Completion rate is calculated among subjects in Full analysis set. Subjects are expected to complete PROs while on treatment.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PROMIS Patient-Reported Outcomes Measurement Information System.
Program: t_cmpl_promis.sas Executed: 14FEB2025 11:08:48

2.1.7.2 PROMIS – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 16.9.1: Instrument completion rate for PROMIS over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)			Placebo (N=74)		
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)
Baseline	71	70 (98.6)	70 (98.6)	74	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	64 (90.1)	64 (90.1)	74	73 (98.6)	73 (98.6)
Cycle 4, Day 28	65	64 (98.5)	64 (98.5)	73	68 (93.2)	68 (93.2)
Cycle 8, Day 28	65	59 (90.8)	59 (90.8)	69	65 (94.2)	65 (94.2)
Cycle 12, Day 28	60	58 (96.7)	58 (96.7)	67	61 (91.0)	61 (91.0)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100 % when
a subject continues to complete after discontinuation.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PROMIS Patient-Reported Outcomes Measurement Information System.
Program: t_cmpl_promis.sas Executed: 14FEB2025 11:08:50

2.1.8 PlexiQoL

2.1.8.1 PlexiQoL – FAS

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 20.8.1: Instrument completion rate for PlexiQoL over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)			Placebo (N=74)		
Timepoint	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	70 (98.6)	70 (98.6)	71 (100)	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	64 (90.1)	64 (90.1)	64 (90.1)	73 (98.6)	73 (98.6)	73 (98.6)
Cycle 4, Day 28	64 (90.1)	64 (90.1)	64 (90.1)	68 (91.9)	68 (91.9)	68 (91.9)
Cycle 8, Day 28	59 (83.1)	59 (83.1)	59 (83.1)	65 (87.8)	65 (87.8)	65 (87.8)
Cycle 12, Day 28	58 (81.7)	58 (81.7)	58 (81.7)	61 (82.4)	61 (82.4)	61 (82.4)

[a] Completion rate is calculated among subjects in Full analysis set. Subjects are expected to complete PROs while on treatment.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PlexiQoL Plexiform Neurofibroma Quality of Life scale.
If >3 items are missing, score is not derived.
Program: t_cmpl_plexi.sas Executed: 03FEB2025 16:45:55

2.1.8.2 PlexiQoL – FAS – bezogen auf alle Patienten unter Behandlung

Protocol Number: D134BC00001 Phase III page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Table 20.9.1: Instrument completion rate for PlexiQoL over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)				Placebo (N=74)			
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	71	70 (98.6)	70 (98.6)	71 (100)	74	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	64 (90.1)	64 (90.1)	64 (90.1)	74	73 (98.6)	73 (98.6)	73 (98.6)
Cycle 4, Day 28	65	64 (98.5)	64 (98.5)	64 (98.5)	73	68 (93.2)	68 (93.2)	68 (93.2)
Cycle 8, Day 28	65	59 (90.8)	59 (90.8)	59 (90.8)	69	65 (94.2)	65 (94.2)	65 (94.2)
Cycle 12, Day 28	60	58 (96.7)	58 (96.7)	58 (96.7)	67	61 (91.0)	61 (91.0)	61 (91.0)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100 % when
a subject continues to complete after discontinuation.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PlexiQoL Plexiform Neurofibroma Quality of Life scale.
If >3 items are missing, score is not derived.
Program: t_cmpl_plexi.sas Executed: 03FEB2025 16:45:56

2.1.9 PedsQL NF1

2.1.9.1 PedsQL NF1 – FAS

Protocol Number: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 19.8.1: Instrument completion rate for PedsQL NF1 module over the randomised period (Full Analysis Set)

	Selumetinib 25 mg/m2 BID (N=71)			Placebo (N=74)		
Timepoint	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	71 (100)	71 (100)	71 (100)	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	64 (90.1)	64 (90.1)	64 (90.1)	73 (98.6)	73 (98.6)	73 (98.6)
Cycle 4, Day 28	64 (90.1)	64 (90.1)	64 (90.1)	68 (91.9)	68 (91.9)	68 (91.9)
Cycle 8, Day 28	59 (83.1)	59 (83.1)	59 (83.1)	65 (87.8)	65 (87.8)	65 (87.8)
Cycle 12, Day 28	58 (81.7)	58 (81.7)	58 (81.7)	61 (82.4)	61 (82.4)	61 (82.4)

[a] Completion rate is calculated among subjects in Full analysis set. Subjects are expected to complete PROs while on treatment.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1 ; Adult version of PedsQL NF1 is used.
If >50% items are missing, score is not derived.
Program: t_cmpl_pedsql.sas Executed: 03FEB2025 16:48:17

2.1.9.2 PedsQL NF1 – FAS – bezogen auf alle Patienten unter Behandlung

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Table 19.9.1: Instrument completion rate for PedsQL NF1 module over the randomised period (Full Analysis Set) - among subjects expected to have an assessment

	Selumetinib 25 mg/m2 BID (N=71)				Placebo (N=74)			
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	71	71 (100)	71 (100)	71 (100)	74	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	64 (90.1)	64 (90.1)	64 (90.1)	74	73 (98.6)	73 (98.6)	73 (98.6)
Cycle 4, Day 28	65	64 (98.5)	64 (98.5)	64 (98.5)	73	68 (93.2)	68 (93.2)	68 (93.2)
Cycle 8, Day 28	65	59 (90.8)	59 (90.8)	59 (90.8)	69	65 (94.2)	65 (94.2)	65 (94.2)
Cycle 12, Day 28	60	58 (96.7)	58 (96.7)	58 (96.7)	67	61 (91.0)	61 (91.0)	61 (91.0)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100 % when
a subject continues to complete after discontinuation.
PRO = Patient-reported outcome ; n = Number of subjects per category ; N = Number of subjects in treatment group from full analysis set.
Full Analysis Set consists of subjects randomised to study intervention in the study.
PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1 ; Adult version of PedsQL NF1 is used.
If >50% items are missing, score is not derived.
Program: t_cmpl_pedsql.sas Executed: 03FEB2025 16:48:19

2.2 Unerwünschte Ereignisse nach SOC und PT

2.2.1 UE jeglichen Schweregrads

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Infections and infestations

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	38 (53.52%)	1.43 (0.74,2.75)	1.20 (0.86,1.68)	0.09 (-0.07,0.25)	0.321
Placebo N=74	33 (44.59%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Infections and infestations PT: COVID-19

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	11 (15.49%)	0.72 (0.31,1.70)	0.76 (0.38,1.55)	-0.05 (-0.17,0.08)	0.519
Placebo N=74	15 (20.27%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Infections and infestations PT: Paronychia

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	9 (12.68%)	3.44 (0.89,13.26)	3.13 (0.88,11.08)	0.09 (0.00,0.18)	0.074
Placebo N=74	3 (4.05%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Blood and lymphatic system disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	8 (11.27%)	0.73 (0.27,1.93)	0.76 (0.32,1.77)	-0.04 (-0.15,0.07)	0.625
Placebo N=74	11 (14.86%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Blood and lymphatic system disorders PT: Anaemia

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	5 (7.04%)	0.63 (0.19,2.01)	0.65 (0.22,1.90)	-0.04 (-0.13,0.05)	0.564
Placebo N=74	8 (10.81%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Metabolism and nutrition disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	7 (9.86%)	0.51 (0.19,1.37)	0.56 (0.24,1.33)	-0.08 (-0.19,0.03)	0.230
Placebo N=74	13 (17.57%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Metabolism and nutrition disorders PT: Decreased appetite

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	1 (1.41%)	0.12 (0.01,0.97)	0.13 (0.02,1.02)	-0.09 (-0.17,-0.02)	0.034
Placebo N=74	8 (10.81%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Nervous system disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	20 (28.17%)	1.06 (0.51,2.19)	1.04 (0.62,1.77)	0.01 (-0.13,0.16)	1.000
Placebo N=74	20 (27.03%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Nervous system disorders PT: Headache

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	8 (11.27%)	0.92 (0.33,2.53)	0.93 (0.38,2.27)	-0.01 (-0.11,0.10)	1.000
Placebo N=74	9 (12.16%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Eye disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	12 (16.90%)	1.47 (0.58,3.74)	1.39 (0.62,3.09)	0.05 (-0.07,0.16)	0.483
Placebo N=74	9 (12.16%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Respiratory/thoracic/mediastinal disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	12 (16.90%)	1.05 (0.44,2.52)	1.04 (0.50,2.16)	0.01 (-0.11,0.13)	1.000
Placebo N=74	12 (16.22%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Gastrointestinal disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	53 (74.65%)	3.86 (1.91,7.82)	1.73 (1.29,2.32)	0.31 (0.16,0.47)	<0.001
Placebo N=74	32 (43.24%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Diarrhoea

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	30 (42.25%)	5.28 (2.28,12.26)	3.47 (1.78,6.79)	0.30 (0.16,0.44)	<0.001
Placebo N=74	9 (12.16%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Nausea

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	18 (25.35%)	1.75 (0.77,3.97)	1.56 (0.81,3.01)	0.09 (-0.04,0.22)	0.220
Placebo N=74	12 (16.22%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Gastrointestinal disorders PT: Vomiting

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	18 (25.35%)	3.85 (1.43,10.37)	3.13 (1.32,7.42)	0.17 (0.05,0.29)	0.007
Placebo N=74	6 (8.11%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	64 (90.14%)	16.88 (6.76,42.13)	2.57 (1.86,3.53)	0.55 (0.42,0.68)	<0.001
Placebo N=74	26 (35.14%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Alopecia

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	13 (18.31%)	1.85 (0.72,4.78)	1.69 (0.75,3.84)	0.07 (-0.04,0.19)	0.242
Placebo N=74	8 (10.81%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dermatitis acneiform

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	42 (59.15%)	11.95 (4.99,28.61)	5.47 (2.77,10.83)	0.48 (0.35,0.62)	<0.001
Placebo N=74	8 (10.81%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Dry skin

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	13 (18.31%)	3.92 (1.21,12.68)	3.39 (1.16,9.90)	0.13 (0.03,0.23)	0.020
Placebo N=74	4 (5.41%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Skin and subcutaneous tissue disorders PT: Rash

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	11 (15.49%)	4.34 (1.16,16.28)	3.82 (1.11,13.13)	0.11 (0.02,0.21)	0.025
Placebo N=74	3 (4.05%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Musculoskeletal and connective tissue disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	19 (26.76%)	1.23 (0.58,2.61)	1.16 (0.66,2.05)	0.04 (-0.10,0.18)	0.701
Placebo N=74	17 (22.97%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Musculoskeletal and connective tissue disorders PT: Arthralgia

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	3 (4.23%)	0.36 (0.09,1.43)	0.39 (0.11,1.41)	-0.07 (-0.15,0.02)	0.209
Placebo N=74	8 (10.81%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Musculoskeletal and connective tissue disorders PT: Pain in extremity

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	5 (7.04%)	0.63 (0.19,2.01)	0.65 (0.22,1.90)	-0.04 (-0.13,0.05)	0.564
Placebo N=74	8 (10.81%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: General disorders and administration site conditions

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	36 (50.70%)	2.60 (1.31,5.16)	1.79 (1.16,2.74)	0.22 (0.07,0.38)	0.007
Placebo N=74	21 (28.38%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:11

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: General disorders and administration site conditions PT: Fatigue

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	14 (19.72%)	1.57 (0.65,3.81)	1.46 (0.69,3.07)	0.06 (-0.06,0.18)	0.375
Placebo N=74	10 (13.51%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:11

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: General disorders and administration site conditions PT: Oedema peripheral

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	11 (15.49%)	13.38 (1.68,106.64)	11.46 (1.52,86.52)	0.14 (0.05,0.23)	0.002
Placebo N=74	1 (1.35%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:11

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Investigations

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	44 (61.97%)	4.11 (2.05,8.25)	2.18 (1.46,3.27)	0.34 (0.18,0.49)	<0.001
Placebo N=74	21 (28.38%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:11

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Investigations PT: Alanine aminotransferase increased

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	11 (15.49%)	2.53 (0.83,7.69)	2.29 (0.84,6.27)	0.09 (-0.01,0.19)	0.115
Placebo N=74	5 (6.76%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:11

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Investigations PT: Aspartate aminotransferase increased

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	13 (18.31%)	3.92 (1.21,12.68)	3.39 (1.16,9.90)	0.13 (0.03,0.23)	0.020
Placebo N=74	4 (5.41%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:11

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	32 (45.07%)	14.36 (4.73,43.60)	8.34 (3.11,22.37)	0.40 (0.27,0.52)	<0.001
Placebo N=74	4 (5.41%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.2.1: Patients with AE by SOC and PT (Randomised Period SAF)
SOC: Injury or poisoning and procedural complications

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	11 (15.49%)	1.32 (0.51,3.42)	1.27 (0.56,2.89)	0.03 (-0.08,0.15)	0.634
Placebo N=74	9 (12.16%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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2.2.2 Schwere UE (CTCAE Grad ≥ 3)

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.4.1: Patients with Severe AE (CTCAE >=3) by SOC and PT (Randomised Period SAF)
SOC: Infections and infestations

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	6 (8.45%)	6.74 (0.79,57.46)	6.25 (0.77,50.65)	0.07 (0.00,0.14)	0.059
Placebo N=74	1 (1.35%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.4.1: Patients with Severe AE (CTCAE >=3) by SOC and PT (Randomised Period SAF)
SOC: Nervous system disorders

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	4 (5.63%)	1.41 (0.30,6.55)	1.39 (0.32,5.99)	0.02 (-0.05,0.09)	0.715
Placebo N=74	3 (4.05%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:13

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.4.1: Patients with Severe AE (CTCAE >=3) by SOC and PT (Randomised Period SAF)
SOC: Investigations

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	10 (14.08%)	11.97 (1.49,96.13)	10.42 (1.37,79.33)	0.13 (0.04,0.21)	0.004
Placebo N=74	1 (1.35%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
Program: t_ae_summary_socpt.sas Executed: 30OCT2025 17:07:13

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 24.4.1: Patients with Severe AE (CTCAE >=3) by SOC and PT (Randomised Period SAF)
SOC: Investigations PT: Blood creatine phosphokinase increased

Treatment group	Subjects with event Number (%) [a]	OR 95% CI	RR 95% CI	RD 95% CI	p-value [b]
Selumetinib 25 mg/m2 BID N=71	5 (7.04%)	5.53 (0.63,48.57)	5.21 (0.62,43.51)	0.06 (-0.01,0.12)	0.111
Placebo N=74	1 (1.35%)				

OR = Odds Ratio; RR = Risk Ratio; RD = Risk Difference; CI = Confidence Interval; SOC = System Organ Class; PT = Preferred Term
[a] Count and proportion of patients who experienced at least one event.
[b] The p-value is based on Fisher's exact test.
N = Number of subjects in treatment group from Randomized Period Safety Analysis Set.
Randomized Period SAF includes subjects who received any amount of study intervention in the randomised period.
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2.2.3 Schwerwiegende unerwünschte Ereignisse (SUE)

Schwellenwert für die Darstellung gemäß Dossiervorlage nicht erreicht.

2.2.4 Abbruch der Studienmedikation aufgrund von UE

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.3.5.1.1 Number of subjects with adverse events leading to discontinuation of study intervention, by system organ class and preferred term (Randomised period safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)
Subjects with any AE leading to discontinuation of study intervention [b]	9 (12.7)	5 (6.8)
Infections and infestations	1 (1.4)	0
Cellulitis	1 (1.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.8)	3 (4.1)
Neurofibrosarcoma	1 (1.4)	3 (4.1)
Neurofibrosarcoma recurrent	1 (1.4)	0
Metabolism and nutrition disorders	0	1 (1.4)
Decreased appetite	0	1 (1.4)
Psychiatric disorders	1 (1.4)	0
Psychiatric decompensation	1 (1.4)	0

[a] Number (%) of subjects with AEs leading to discontinuation of study intervention, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs leading to discontinuation of study intervention are counted once for each system organ class/preferred term. [b] Action taken, Drug Permanently Discontinued. Includes only AEs that are treatment emergent during the randomised period.
Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 26.1. Randomised period safety analysis set - subjects who received any amount of study intervention in the randomised period. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after

discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.3.5.1.1 Number of subjects with adverse events leading to discontinuation of study intervention, by system organ class and preferred term (Randomised period safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)
Eye disorders	1 (1.4)	0
Ulcerative keratitis	1 (1.4)	0
Gastrointestinal disorders	1 (1.4)	1 (1.4)
Nausea	1 (1.4)	0
Stomatitis	0	1 (1.4)
Skin and subcutaneous tissue disorders	3 (4.2)	0
Dermatitis acneiform	2 (2.8)	0
Nail disorder	1 (1.4)	0
Injury, poisoning and procedural complications	1 (1.4)	0
Wound	1 (1.4)	0

[a] Number (%) of subjects with AEs leading to discontinuation of study intervention, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs leading to discontinuation of study intervention are counted once for each system organ class/preferred term. [b] Action taken, Drug Permanently Discontinued. Includes only AEs that are treatment emergent during the randomised period.
Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 26.1. Randomised period safety analysis set - subjects who received any amount of study intervention in the randomised period. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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2.3 Werte im Studienverlauf

2.3.1 PAINS-pNF

2.3.1.1 PAINS-pNF, chronischer Schmerz

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	71 (100)	4.18 (2.52)							
	Placebo, N=74	74 (100)	4.33 (2.71)							
Cycle 1	Selumetinib 25 mg/m2 BID, N=71	68 (95.77)	3.69 (2.55)	68 (95.77)	-0.59 (0.13)	(-0.85, -0.34)	-0.22	(-0.55, 0.10)	0.181	
	Placebo, N=74	74 (100)	4.03 (2.81)	74 (100)	-0.37 (0.12)	(-0.61, -0.13)				
Cycle 2	Selumetinib 25 mg/m2 BID, N=71	67 (94.37)	3.52 (2.56)	67 (94.37)	-0.81 (0.17)	(-1.15, -0.47)	-0.23	(-0.68, 0.22)	0.317	
	Placebo, N=74	74 (100)	3.81 (2.76)	74 (100)	-0.59 (0.16)	(-0.91, -0.27)				
Cycle 3	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	3.40 (2.53)	65 (91.55)	-1.03 (0.18)	(-1.39, -0.67)	-0.39	(-0.87, 0.09)	0.113	
	Placebo, N=74	73 (98.65)	3.70 (2.73)	73 (98.65)	-0.64 (0.17)	(-0.98, -0.30)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN)
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is derived as average of daily scores during screening period, if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods.
Post-baseline score is derived as average of daily scores within 28-day cycles, if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods of the cycle.
A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	– (95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 4	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	3.16 (2.40)	65 (91.55)	-1.26 (0.19)	(-1.65, -0.88)	-0.55	(-1.07, -0.04)	0.036	-0.36 (-0.70, -0.02)
	Placebo, N=74	71 (95.95)	3.60 (2.79)	71 (95.95)	-0.71 (0.18)	(-1.08, -0.35)				
Cycle 5	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	3.14 (2.37)	65 (91.55)	-1.29 (0.20)	(-1.69, -0.89)	-0.40	(-0.94, 0.14)	0.143	
	Placebo, N=74	69 (93.24)	3.34 (2.75)	69 (93.24)	-0.89 (0.19)	(-1.27, -0.51)				
Cycle 6	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	3.01 (2.34)	64 (90.14)	-1.36 (0.20)	(-1.75, -0.96)	-0.42	(-0.95, 0.11)	0.116	
	Placebo, N=74	69 (93.24)	3.38 (2.73)	69 (93.24)	-0.93 (0.19)	(-1.31, -0.56)				
Cycle 7	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	2.77 (2.31)	59 (83.10)	-1.57 (0.21)	(-1.99, -1.16)	-0.62	(-1.17, -0.06)	0.029	-0.37 (-0.73, -0.02)
	Placebo, N=74	68 (91.89)	3.29 (2.71)	68 (91.89)	-0.96 (0.20)	(-1.35, -0.56)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN)
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is derived as average of daily scores during screening period, if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods.
Post-baseline score is derived as average of daily scores within 28-day cycles, if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods of the cycle.
A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 8	Selumetinib 25 mg/m2 BID, N=71	60 (84.51)	2.88 (2.41)	60 (84.51)	-1.44 (0.22)	(-1.87, -1.01)	-0.49	(-1.07, 0.09)	0.100	
	Placebo, N=74	66 (89.19)	3.30 (2.75)	66 (89.19)	-0.95 (0.21)	(-1.36, -0.54)				
Cycle 9	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	2.83 (2.38)	59 (83.10)	-1.45 (0.21)	(-1.87, -1.03)	-0.61	(-1.17, -0.04)	0.036	-0.37 (-0.73, -0.01)
	Placebo, N=74	65 (87.84)	3.31 (2.70)	65 (87.84)	-0.85 (0.20)	(-1.25, -0.45)				
Cycle 10	Selumetinib 25 mg/m2 BID, N=71	60 (84.51)	2.83 (2.41)	60 (84.51)	-1.50 (0.21)	(-1.92, -1.08)	-0.51	(-1.07, 0.05)	0.076	
	Placebo, N=74	64 (86.49)	3.14 (2.69)	64 (86.49)	-0.99 (0.20)	(-1.39, -0.59)				
Cycle 11	Selumetinib 25 mg/m2 BID, N=71	55 (77.46)	2.67 (2.36)	55 (77.46)	-1.60 (0.22)	(-2.03, -1.17)	-0.64	(-1.21, -0.06)	0.030	-0.39 (-0.76, -0.02)
	Placebo, N=74	63 (85.14)	3.10 (2.71)	63 (85.14)	-0.96 (0.21)	(-1.37, -0.56)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN)
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is derived as average of daily scores during screening period, if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods.
Post-baseline score is derived as average of daily scores within 28-day cycles, if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods of the cycle.
A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.10.1: Pains-pNF, Chronic Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 12	Selumetinib 25 mg/m2 BID, N=71	57 (80.28)	2.73 (2.40)	57 (80.28)	-1.59 (0.22)	(-2.03, -1.15)	-0.69	(-1.29, -0.09)	0.024	-0.42 (-0.78, -0.05)
	Placebo, N=74	62 (83.78)	3.07 (2.61)	62 (83.78)	-0.90 (0.21)	(-1.32, -0.47)				
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	68 (95.77)	3.07 (2.43)	68 (95.77)	-1.29 (0.18)	(-1.65, -0.93)	-0.48	(-0.95, -0.01)	0.048	-0.33 (-0.66, 0.01)
	Placebo, N=74	74 (100)	3.44 (2.73)	74 (100)	-0.81 (0.17)	(-1.15, -0.47)				

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN)
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is derived as average of daily scores during screening period, if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods.
Post-baseline score is derived as average of daily scores within 28-day cycles, if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods of the cycle.
A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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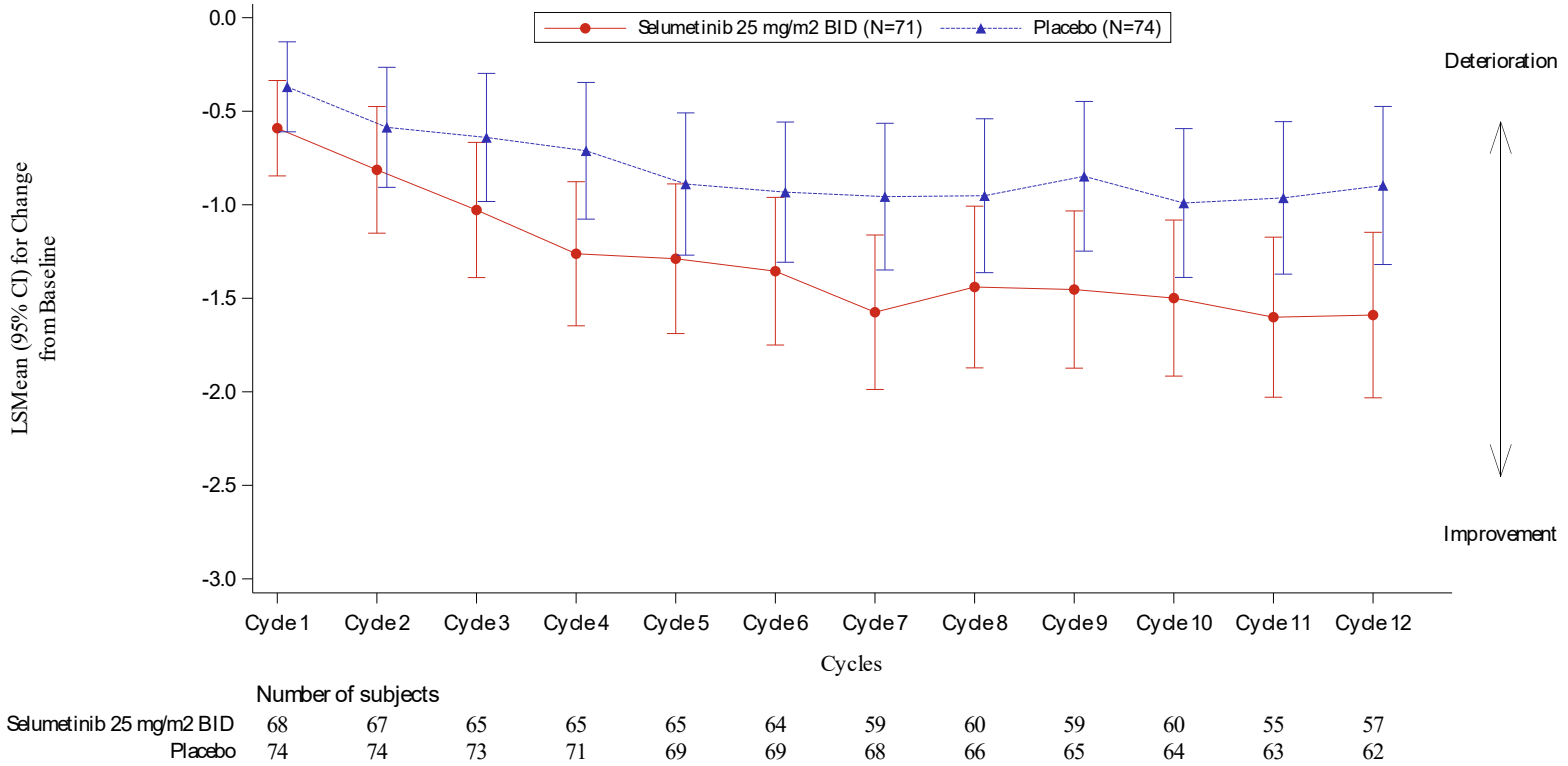
Figure 14.10.1.3: Pains-pNF, Chronic Pain: LS Mean change from baseline (Full Analysis Set)



PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN).
N = Number of subjects in treatment group, LS = Least Square, CI = Confidence Interval
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means on the treatment group*cycle interaction are plotted. Error bars represent 95% CIs.
Full analysis set - subjects randomised to study intervention
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2.3.1.2 PAINS-pNF, Schmerzspitze

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	71 (100)	6.59 (2.62)							
	Placebo, N=74	74 (100)	6.34 (3.00)							
Cycle 1	Selumetinib 25 mg/m2 BID, N=71	71 (100)	5.93 (2.76)	71 (100)	-0.61 (0.21)	(-1.02, -0.19)	-0.16	(-0.71, 0.38)	0.551	
	Placebo, N=74	74 (100)	5.88 (3.04)	74 (100)	-0.44 (0.21)	(-0.85, -0.04)				
Cycle 2	Selumetinib 25 mg/m2 BID, N=71	68 (95.77)	5.29 (2.95)	68 (95.77)	-1.24 (0.23)	(-1.68, -0.79)	-0.47	(-1.05, 0.11)	0.111	
	Placebo, N=74	74 (100)	5.55 (3.04)	74 (100)	-0.77 (0.22)	(-1.19, -0.34)				
Cycle 3	Selumetinib 25 mg/m2 BID, N=71	67 (94.37)	5.01 (2.84)	67 (94.37)	-1.56 (0.23)	(-2.01, -1.11)	-0.52	(-1.11, 0.07)	0.086	
	Placebo, N=74	73 (98.65)	5.23 (3.10)	73 (98.65)	-1.04 (0.22)	(-1.48, -0.61)				

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PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN).
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in a 28-day cycle.
A higher PAINS-pNF spike pain score is worse. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 4	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	4.68 (2.88)	65 (91.55)	-1.97 (0.25)	(-2.46, -1.49)	-0.62	(-1.26, 0.02)	0.057	
	Placebo, N=74	72 (97.30)	4.88 (3.03)	72 (97.30)	-1.36 (0.24)	(-1.82, -0.89)				
Cycle 5	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	4.60 (2.80)	65 (91.55)	-2.04 (0.27)	(-2.58, -1.50)	-0.72	(-1.44, 0.00)	0.049	-0.33 (-0.67, 0.01)
	Placebo, N=74	70 (94.59)	4.94 (3.22)	70 (94.59)	-1.32 (0.26)	(-1.84, -0.80)				
Cycle 6	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	4.60 (2.93)	65 (91.55)	-2.04 (0.26)	(-2.56, -1.52)	-0.67	(-1.37, 0.02)	0.056	
	Placebo, N=74	70 (94.59)	4.89 (3.09)	70 (94.59)	-1.37 (0.25)	(-1.86, -0.87)				
Cycle 7	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	4.40 (2.87)	65 (91.55)	-2.23 (0.27)	(-2.77, -1.70)	-0.58	(-1.29, 0.12)	0.104	
	Placebo, N=74	69 (93.24)	4.57 (3.14)	69 (93.24)	-1.65 (0.26)	(-2.16, -1.14)				

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PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN).
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in a 28-day cycle.
A higher PAINS-pNF spike pain score is worse. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 8	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	4.33 (2.90)	64 (90.14)	-2.25 (0.27)	(-2.78, -1.72)	-0.71	(-1.41, -0.01)	0.048	-0.33 (-0.67, 0.02)
	Placebo, N=74	69 (93.24)	4.67 (3.12)	69 (93.24)	-1.54 (0.26)	(-2.05, -1.04)				
Cycle 9	Selumetinib 25 mg/m2 BID, N=71	62 (87.32)	4.21 (2.98)	62 (87.32)	-2.29 (0.29)	(-2.86, -1.71)	-0.74	(-1.52, 0.03)	0.060	
	Placebo, N=74	66 (89.19)	4.61 (3.22)	66 (89.19)	-1.54 (0.28)	(-2.10, -0.99)				
Cycle 10	Selumetinib 25 mg/m2 BID, N=71	61 (85.92)	4.31 (2.81)	61 (85.92)	-2.15 (0.28)	(-2.70, -1.59)	-0.69	(-1.43, 0.05)	0.065	
	Placebo, N=74	66 (89.19)	4.70 (3.25)	66 (89.19)	-1.45 (0.27)	(-1.98, -0.92)				
Cycle 11	Selumetinib 25 mg/m2 BID, N=71	60 (84.51)	4.27 (2.90)	60 (84.51)	-2.19 (0.29)	(-2.76, -1.61)	-0.55	(-1.32, 0.23)	0.164	
	Placebo, N=74	65 (87.84)	4.49 (3.25)	65 (87.84)	-1.64 (0.28)	(-2.20, -1.09)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN).
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in a 28-day cycle.
A higher PAINS-pNF spike pain score is worse. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.1: Pains-pNF, Spike Pain: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 12	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	4.02 (2.95)	58 (81.69)	-2.53 (0.29)	(-3.11, -1.95)	-1.06	(-1.84, -0.27)	0.009	-0.48 (-0.84, -0.11)
	Placebo, N=74	64 (86.49)	4.58 (3.30)	64 (86.49)	-1.47 (0.28)	(-2.03, -0.92)				
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	71 (100)	4.66 (2.91)	71 (100)	-1.92 (0.22)	(-2.37, -1.48)	-0.62	(-1.20, -0.05)	0.033	-0.34 (-0.67, -0.01)
	Placebo, N=74	74 (100)	4.93 (3.15)	74 (100)	-1.30 (0.21)	(-1.72, -0.88)				

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN).
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in a 28-day cycle.
A higher PAINS-pNF spike pain score is worse. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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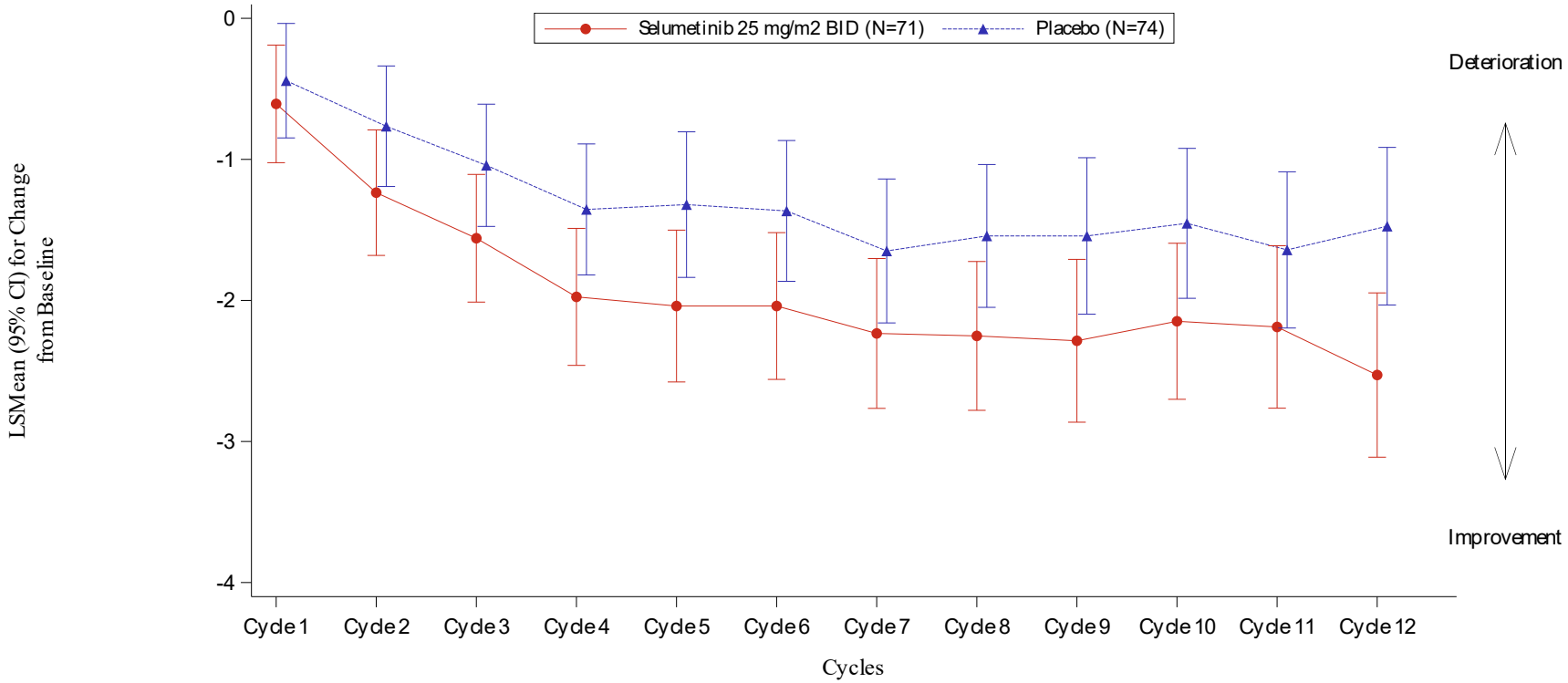
Figure 14.1.1.3: Pains-pNF, Spike Pain : LS Mean change from baseline (Full Analysis Set)



Number of subjects												
Selumetinib 25 mg/m2 BID	71	68	67	65	65	65	65	64	62	61	60	58
Placebo	74	74	73	72	70	70	69	69	66	66	65	64

PAINS-pNF= Pain Intensity Scale for Plexiform Neurofibroma (PN).
N = Number of subjects in treatment group, LS = Least Square, CI = Confidence Interval
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means on the treatement group*cycle interaction are plotted. Error bars represent 95% CIs.
Full analysis set - subjects randomised to study intervention
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2.3.2 PGIC

2.3.2.1 PGIC, chronischer Schmerz und Schmerzspitze

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Since last visit	Cycle 1, Day 28	Much better	5 (7.5)	3 (4.1)
			Moderately better	10 (14.9)	2 (2.7)
			A little better	18 (26.9)	14 (18.9)
			About the same/No change	31 (46.3)	48 (64.9)
			A little worse	1 (1.5)	6 (8.1)
			Moderately worse	2 (3.0)	1 (1.4)
			Much worse	0	0
			Total non-missing	67	74
		Cycle 2, Day 28	Much better	6 (9.2)	4 (5.5)
			Moderately better	10 (15.4)	5 (6.8)
			A little better	18 (27.7)	15 (20.5)
			About the same/No change	26 (40.0)	40 (54.8)
			A little worse	4 (6.2)	7 (9.6)
			Moderately worse	0	2 (2.7)
			Much worse	1 (1.5)	0
			Total non-missing	65	73

Study Code: D134BC00001 Phase III
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Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Since last visit	Cycle 4, Day 28	Much better	7 (10.9)	3 (4.4)
			Moderately better	12 (18.8)	6 (8.8)
			A little better	15 (23.4)	14 (20.6)
			About the same/No change	27 (42.2)	39 (57.4)
			A little worse	1 (1.6)	5 (7.4)
			Moderately worse	2 (3.1)	1 (1.5)
			Much worse	0	0
			Total non-missing	64	68
		Cycle 6, Day 28	Much better	8 (12.5)	10 (14.9)
			Moderately better	13 (20.3)	5 (7.5)
			A little better	10 (15.6)	9 (13.4)
			About the same/No change	26 (40.6)	35 (52.2)
			A little worse	4 (6.3)	7 (10.4)
			Moderately worse	2 (3.1)	1 (1.5)
			Much worse	1 (1.6)	0
			Total non-missing	64	67

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Since last visit	Cycle 8, Day 28	Much better	10 (17.2)	5 (7.8)
			Moderately better	6 (10.3)	7 (10.9)
			A little better	8 (13.8)	12 (18.8)
			About the same/No change	27 (46.6)	30 (46.9)
			A little worse	3 (5.2)	8 (12.5)
			Moderately worse	4 (6.9)	2 (3.1)
			Much worse	0	0
			Total non-missing	58	64
		Cycle 10, Day 28	Much better	9 (15.5)	8 (13.3)
			Moderately better	6 (10.3)	7 (11.7)
			A little better	12 (20.7)	7 (11.7)
			About the same/No change	26 (44.8)	30 (50.0)
			A little worse	3 (5.2)	5 (8.3)
			Moderately worse	2 (3.4)	1 (1.7)
			Much worse	0	2 (3.3)
			Total non-missing	58	60

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Program: t_pgis_dist.sas Executed: 10OCT2025 13:38:32

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Since last visit	Cycle 12, Day 28	Much better	7 (12.3)	5 (8.6)
			Moderately better	9 (15.8)	4 (6.9)
			A little better	9 (15.8)	3 (5.2)
			About the same/No change	27 (47.4)	36 (62.1)
			A little worse	3 (5.3)	7 (12.1)
			Moderately worse	1 (1.8)	3 (5.2)
			Much worse	1 (1.8)	0
			Total non-missing	57	58
	Since first dose	Cycle 2, Day 28	Much better	0	0
			Moderately better	0	0
			A little better	0	0
			About the same/No change	1 (100)	0
			A little worse	0	0
			Moderately worse	0	0
			Much worse	0	0
			Total non-missing	1	0

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Since first dose	Cycle 8, Day 28	Much better	1 (50.0)	1 (33.3)
			Moderately better	0	1 (33.3)
			A little better	1 (50.0)	1 (33.3)
			About the same/No change	0	0
			A little worse	0	0
			Moderately worse	0	0
			Much worse	0	0
			Total non-missing	2	3
		Cycle 12, Day 28	Much better	14 (24.6)	7 (12.1)
			Moderately better	11 (19.3)	3 (5.2)
			A little better	10 (17.5)	7 (12.1)
			About the same/No change	19 (33.3)	32 (55.2)
			A little worse	2 (3.5)	6 (10.3)
			Moderately worse	1 (1.8)	3 (5.2)
			Much worse	0	0
			Total non-missing	57	58

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Program: t_pgis_dist.sas Executed: 10OCT2025 13:38:32

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Since last visit	Cycle 1, Day 28	Much better	6 (9.0)	4 (5.4)
			Moderately better	8 (11.9)	3 (4.1)
			A little better	21 (31.3)	15 (20.3)
			About the same/No change	27 (40.3)	47 (63.5)
			A little worse	3 (4.5)	3 (4.1)
			Moderately worse	2 (3.0)	2 (2.7)
			Much worse	0	0
			Total non-missing	67	74
		Cycle 2, Day 28	Much better	6 (9.2)	4 (5.5)
			Moderately better	14 (21.5)	5 (6.8)
			A little better	13 (20.0)	15 (20.5)
			About the same/No change	27 (41.5)	41 (56.2)
			A little worse	2 (3.1)	1 (1.4)
			Moderately worse	2 (3.1)	7 (9.6)
			Much worse	1 (1.5)	0
			Total non-missing	65	73

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Program: t_pgis_dist.sas Executed: 10OCT2025 13:38:32

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Since last visit	Cycle 4, Day 28	Much better	6 (9.4)	3 (4.4)
			Moderately better	11 (17.2)	7 (10.3)
			A little better	22 (34.4)	11 (16.2)
			About the same/No change	22 (34.4)	40 (58.8)
			A little worse	2 (3.1)	5 (7.4)
			Moderately worse	1 (1.6)	1 (1.5)
			Much worse	0	1 (1.5)
			Total non-missing	64	68
		Cycle 6, Day 28	Much better	6 (9.4)	8 (11.9)
			Moderately better	13 (20.3)	5 (7.5)
			A little better	14 (21.9)	13 (19.4)
			About the same/No change	24 (37.5)	33 (49.3)
			A little worse	4 (6.3)	7 (10.4)
			Moderately worse	2 (3.1)	0
			Much worse	1 (1.6)	1 (1.5)
			Total non-missing	64	67

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Since last visit	Cycle 8, Day 28	Much better	9 (15.5)	6 (9.4)
			Moderately better	7 (12.1)	5 (7.8)
			A little better	9 (15.5)	10 (15.6)
			About the same/No change	26 (44.8)	34 (53.1)
			A little worse	5 (8.6)	5 (7.8)
			Moderately worse	2 (3.4)	3 (4.7)
			Much worse	0	1 (1.6)
			Total non-missing	58	64
		Cycle 10, Day 28	Much better	8 (13.8)	10 (16.7)
			Moderately better	6 (10.3)	4 (6.7)
			A little better	11 (19.0)	5 (8.3)
			About the same/No change	27 (46.6)	34 (56.7)
			A little worse	3 (5.2)	4 (6.7)
			Moderately worse	3 (5.2)	2 (3.3)
			Much worse	0	1 (1.7)
			Total non-missing	58	60

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Since last visit	Cycle 12, Day 28	Much better	6 (10.5)	4 (6.9)
			Moderately better	11 (19.3)	5 (8.6)
			A little better	6 (10.5)	2 (3.4)
			About the same/No change	28 (49.1)	38 (65.5)
			A little worse	4 (7.0)	9 (15.5)
			Moderately worse	1 (1.8)	0
			Much worse	1 (1.8)	0
			Total non-missing	57	58
	Since first dose	Cycle 2, Day 28	Much better	0	0
			Moderately better	0	0
			A little better	0	0
			About the same/No change	1 (100)	0
			A little worse	0	0
			Moderately worse	0	0
			Much worse	0	0
			Total non-missing	1	0

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 17.1.1 Distribution of Patient Global Impression of Change (PGIC) responses over time during the randomised period (Full analysis set)

				PGIC Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Since first dose	Cycle 8, Day 28	Much better	1 (50.0)	1 (33.3)
			Moderately better	0	1 (33.3)
			A little better	1 (50.0)	1 (33.3)
			About the same/No change	0	0
			A little worse	0	0
			Moderately worse	0	0
			Much worse	0	0
			Total non-missing	2	3
		Cycle 12, Day 28	Much better	12 (21.1)	7 (12.1)
			Moderately better	15 (26.3)	3 (5.2)
			A little better	7 (12.3)	8 (13.8)
			About the same/No change	20 (35.1)	29 (50.0)
			A little worse	1 (1.8)	8 (13.8)
			Moderately worse	2 (3.5)	3 (5.2)
			Much worse	0	0
			Total non-missing	57	58

N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing).
Full analysis set consists of subjects randomised to study intervention in the study.
Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
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2.3.3 PGIS

2.3.3.1 PGIS chronischer Schmerz und Schmerzspitze – Verteilungstabelle

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Past 7 days	Baseline	No pain	10 (14.3)	13 (18.1)
			Mild	18 (25.7)	15 (20.8)
			Moderate	35 (50.0)	31 (43.1)
			Severe	7 (10.0)	13 (18.1)
			Total non-missing	70	72
		Cycle 1, Day 28	No pain	9 (13.4)	16 (21.6)
			Mild	27 (40.3)	16 (21.6)
			Moderate	27 (40.3)	36 (48.6)
			Severe	4 (6.0)	6 (8.1)
			Total non-missing	67	74
		Cycle 2, Day 28	No pain	12 (18.5)	16 (21.9)
			Mild	34 (52.3)	17 (23.3)
			Moderate	16 (24.6)	34 (46.6)
			Severe	3 (4.6)	6 (8.2)
			Total non-missing	65	73

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)

Baseline is defined as the last result obtained prior to the start of the randomised period.
N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
Randomised period - first dose date until earliest of; last dose of cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Past 7 days	Cycle 4, Day 28	No pain	13 (20.3)	16 (23.5)
			Mild	31 (48.4)	16 (23.5)
			Moderate	20 (31.3)	35 (51.5)
			Severe	0	1 (1.5)
			Total non-missing	64	68
		Cycle 6, Day 28	No pain	10 (15.6)	20 (29.9)
			Mild	37 (57.8)	17 (25.4)
			Moderate	16 (25.0)	29 (43.3)
			Severe	1 (1.6)	1 (1.5)
			Total non-missing	64	67
		Cycle 8, Day 28	No pain	10 (17.2)	17 (26.6)
			Mild	31 (53.4)	17 (26.6)
			Moderate	16 (27.6)	27 (42.2)
			Severe	1 (1.7)	3 (4.7)
			Total non-missing	58	64

Baseline is defined as the last result obtained prior to the start of the randomised period.
N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
Randomised period - first dose date until earliest of; last dose of cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
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Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Chronic Pain	Past 7 days	Cycle 10, Day 28	No pain	11 (19.0)	22 (36.7)
			Mild	31 (53.4)	18 (30.0)
			Moderate	12 (20.7)	14 (23.3)
			Severe	4 (6.9)	6 (10.0)
			Total non-missing	58	60
		Cycle 12, Day 28	No pain	11 (19.3)	17 (29.3)
			Mild	34 (59.6)	15 (25.9)
			Moderate	10 (17.5)	23 (39.7)
			Severe	2 (3.5)	3 (5.2)
			Total non-missing	57	58
Spike Pain	Past 7 days	Baseline	No pain	5 (7.1)	9 (12.5)
			Mild	14 (20.0)	15 (20.8)
			Moderate	36 (51.4)	24 (33.3)
			Severe	15 (21.4)	24 (33.3)
			Total non-missing	70	72

Baseline is defined as the last result obtained prior to the start of the randomised period.
N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
Randomised period - first dose date until earliest of; last dose of cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
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Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Past 7 days	Cycle 1, Day 28	No pain	7 (10.4)	12 (16.2)
			Mild	24 (35.8)	20 (27.0)
			Moderate	29 (43.3)	32 (43.2)
			Severe	7 (10.4)	10 (13.5)
			Total non-missing	67	74
		Cycle 2, Day 28	No pain	8 (12.3)	11 (15.1)
			Mild	29 (44.6)	22 (30.1)
			Moderate	22 (33.8)	26 (35.6)
			Severe	6 (9.2)	14 (19.2)
			Total non-missing	65	73
		Cycle 4, Day 28	No pain	9 (14.1)	13 (19.1)
			Mild	34 (53.1)	16 (23.5)
			Moderate	18 (28.1)	26 (38.2)
			Severe	3 (4.7)	13 (19.1)
			Total non-missing	64	68

Baseline is defined as the last result obtained prior to the start of the randomised period.
N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
Randomised period - first dose date until earliest of; last dose of cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Past 7 days	Cycle 6, Day 28	No pain	10 (15.6)	15 (22.4)
			Mild	32 (50.0)	18 (26.9)
			Moderate	19 (29.7)	25 (37.3)
			Severe	3 (4.7)	9 (13.4)
			Total non-missing	64	67
		Cycle 8, Day 28	No pain	12 (20.7)	12 (18.8)
			Mild	27 (46.6)	23 (35.9)
			Moderate	17 (29.3)	19 (29.7)
			Severe	2 (3.4)	10 (15.6)
			Total non-missing	58	64
		Cycle 10, Day 28	No pain	10 (17.2)	15 (25.0)
			Mild	31 (53.4)	17 (28.3)
			Moderate	15 (25.9)	19 (31.7)
			Severe	2 (3.4)	9 (15.0)
			Total non-missing	58	60

Baseline is defined as the last result obtained prior to the start of the randomised period.
N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
Randomised period - first dose date until earliest of; last dose of cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.26.1: Distribution of Patient Global Impression of Severity (PGIS) responses over time during the randomised period (Full Analysis Set)

				Number (%) of subjects	
Item	Reference Period	Timepoint	Response Category	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Spike Pain	Past 7 days	Cycle 12, Day 28	No pain	12 (21.1)	15 (25.9)
			Mild	25 (43.9)	15 (25.9)
			Moderate	18 (31.6)	21 (36.2)
			Severe	2 (3.5)	7 (12.1)
			Total non-missing	57	58

Baseline is defined as the last result obtained prior to the start of the randomised period.
N = Number of subjects in treatment group from full analysis set
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
Randomised period - first dose date until earliest of; last dose of cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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2.3.3.2 PGIS, chronischer Schmerz – Verschiebungstabelle

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.1.1: PGIS, Chronic Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for chronic pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total
Cycle 1, Day 28	No pain	7 (10.61)	1 (1.52)	1 (1.52)	0	9 (13.64)	11 (15.28)	2 (2.78)	1 (1.39)	1 (1.39)	15 (20.83)
	Mild	3 (4.55)	12 (18.18)	12 (18.18)	0	27 (40.91)	2 (2.78)	8 (11.11)	6 (8.33)	0	16 (22.22)
	Moderate	0	2 (3.03)	19 (28.79)	6 (9.09)	27 (40.91)	0	5 (6.94)	21 (29.17)	9 (12.5)	35 (48.61)
	Severe	0	0	2 (3.03)	1 (1.52)	3 (4.55)	0	0	3 (4.17)	3 (4.17)	6 (8.33)
	Total	10 (15.15)	15 (22.73)	34 (51.52)	7 (10.61)	66 (100)	13 (18.06)	15 (20.83)	31 (43.06)	13 (18.06)	72 (100)
Cycle 2, Day 28	No pain	8 (12.5)	2 (3.13)	2 (3.13)	0	12 (18.75)	12 (16.9)	1 (1.41)	1 (1.41)	1 (1.41)	15 (21.13)
	Mild	2 (3.13)	11 (17.19)	20 (31.25)	0	33 (51.56)	1 (1.41)	10 (14.08)	5 (7.04)	1 (1.41)	17 (23.94)
	Moderate	0	1 (1.56)	12 (18.75)	3 (4.69)	16 (25)	0	3 (4.23)	23 (32.39)	7 (9.86)	33 (46.48)
	Severe	0	0	0	3 (4.69)	3 (4.69)	0	1 (1.41)	2 (2.82)	3 (4.23)	6 (8.45)
	Total	10 (15.63)	14 (21.88)	34 (53.13)	6 (9.38)	64 (100)	13 (18.31)	15 (21.13)	31 (43.66)	12 (16.9)	71 (100)
Cycle 4, Day 28	No pain	8 (12.7)	2 (3.17)	2 (3.17)	1 (1.59)	13 (20.63)	9 (13.64)	4 (6.06)	1 (1.52)	1 (1.52)	15 (22.73)
	Mild	1 (1.59)	10 (15.87)	19 (30.16)	0	30 (47.62)	2 (3.03)	7 (10.61)	7 (10.61)	0	16 (24.24)
	Moderate	0	2 (3.17)	13 (20.63)	5 (7.94)	20 (31.75)	1 (1.52)	4 (6.06)	19 (28.79)	10 (15.15)	34 (51.52)
	Severe	0	0	0	0	0	0	0	1 (1.52)	0	1 (1.52)
	Total	9 (14.29)	14 (22.22)	34 (53.97)	6 (9.52)	63 (100)	12 (18.18)	15 (22.73)	28 (42.42)	11 (16.67)	66 (100)

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.1.1: PGIS, Chronic Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for chronic pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total

N = Number of subjects in treatment group from full analysis set
PGIS = Patient Global Impression of Severity
Baseline is defined as the last result obtained prior to the start of the randomised period. Percentages are calculated using the number of subjects with a baseline value and a value
at respective post-baseline visit.
Full analysis set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
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Table 18.1.1: PGIS, Chronic Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for chronic pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total
Cycle 6, Day 28	No pain	6 (9.52)	3 (4.76)	1 (1.59)	0	10 (15.87)	10 (15.38)	4 (6.15)	4 (6.15)	1 (1.54)	19 (29.23)
	Mild	3 (4.76)	10 (15.87)	22 (34.92)	1 (1.59)	36 (57.14)	1 (1.54)	6 (9.23)	7 (10.77)	2 (3.08)	16 (24.62)
	Moderate	0	1 (1.59)	10 (15.87)	5 (7.94)	16 (25.4)	1 (1.54)	4 (6.15)	18 (27.69)	6 (9.23)	29 (44.62)
	Severe	0	0	1 (1.59)	0	1 (1.59)	0	1 (1.54)	0	0	1 (1.54)
	Total	9 (14.29)	14 (22.22)	34 (53.97)	6 (9.52)	63 (100)	12 (18.46)	15 (23.08)	29 (44.62)	9 (13.85)	65 (100)
Cycle 8, Day 28	No pain	5 (8.77)	3 (5.26)	2 (3.51)	0	10 (17.54)	11 (17.74)	3 (4.84)	1 (1.61)	1 (1.61)	16 (25.81)
	Mild	3 (5.26)	9 (15.79)	17 (29.82)	2 (3.51)	31 (54.39)	1 (1.61)	5 (8.06)	10 (16.13)	1 (1.61)	17 (27.42)
	Moderate	0	1 (1.75)	12 (21.05)	2 (3.51)	15 (26.32)	0	6 (9.68)	13 (20.97)	7 (11.29)	26 (41.94)
	Severe	0	0	1 (1.75)	0	1 (1.75)	0	1 (1.61)	2 (3.23)	0	3 (4.84)
	Total	8 (14.04)	13 (22.81)	32 (56.14)	4 (7.02)	57 (100)	12 (19.35)	15 (24.19)	26 (41.94)	9 (14.52)	62 (100)
Cycle 10, Day 28	No pain	6 (10.53)	3 (5.26)	1 (1.75)	1 (1.75)	11 (19.3)	11 (18.97)	4 (6.9)	4 (6.9)	2 (3.45)	21 (36.21)
	Mild	3 (5.26)	9 (15.79)	18 (31.58)	0	30 (52.63)	0	6 (10.34)	9 (15.52)	2 (3.45)	17 (29.31)
	Moderate	0	1 (1.75)	8 (14.04)	3 (5.26)	12 (21.05)	0	3 (5.17)	10 (17.24)	1 (1.72)	14 (24.14)
	Severe	0	0	3 (5.26)	1 (1.75)	4 (7.02)	0	1 (1.72)	3 (5.17)	2 (3.45)	6 (10.34)
	Total	9 (15.79)	13 (22.81)	30 (52.63)	5 (8.77)	57 (100)	11 (18.97)	14 (24.14)	26 (44.83)	7 (12.07)	58 (100)

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.1.1: PGIS, Chronic Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for chronic pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total

N = Number of subjects in treatment group from full analysis set
PGIS = Patient Global Impression of Severity
Baseline is defined as the last result obtained prior to the start of the randomised period. Percentages are calculated using the number of subjects with a baseline value and a value
at respective post-baseline visit.
Full analysis set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 18.1.1: PGIS, Chronic Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for chronic pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total
Cycle 12, Day 28	No pain	5 (8.93)	4 (7.14)	1 (1.79)	1 (1.79)	11 (19.64)	10 (17.86)	3 (5.36)	2 (3.57)	1 (1.79)	16 (28.57)
	Mild	3 (5.36)	10 (17.86)	19 (33.93)	1 (1.79)	33 (58.93)	1 (1.79)	7 (12.5)	4 (7.14)	3 (5.36)	15 (26.79)
	Moderate	0	0	7 (12.5)	3 (5.36)	10 (17.86)	0	3 (5.36)	17 (30.36)	2 (3.57)	22 (39.29)
	Severe	0	0	2 (3.57)	0	2 (3.57)	0	0	1 (1.79)	2 (3.57)	3 (5.36)
	Total	8 (14.29)	14 (25)	29 (51.79)	5 (8.93)	56 (100)	11 (19.64)	13 (23.21)	24 (42.86)	8 (14.29)	56 (100)

N = Number of subjects in treatment group from full analysis set
PGIS = Patient Global Impression of Severity
Baseline is defined as the last result obtained prior to the start of the randomised period. Percentages are calculated using the number of subjects with a baseline value and a value
at respective post-baseline visit.
Full analysis set consists of subjects randomised to study intervention in the study.
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2.3.3.3 PGIS, Schmerzspitze – Verschiebungstabelle

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
18.10.1: PGIS, Spikes of Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for spike pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total
Cycle 1, Day 28	No pain	2 (3.03)	4 (6.06)	1 (1.52)	0	7 (10.61)	8 (11.11)	1 (1.39)	0	2 (2.78)	11 (15.28)
	Mild	3 (4.55)	5 (7.58)	16 (24.24)	0	24 (36.36)	1 (1.39)	11 (15.28)	7 (9.72)	1 (1.39)	20 (27.78)
	Moderate	0	2 (3.03)	18 (27.27)	9 (13.64)	29 (43.94)	0	2 (2.78)	16 (22.22)	14 (19.44)	32 (44.44)
	Severe	0	0	1 (1.52)	5 (7.58)	6 (9.09)	0	1 (1.39)	1 (1.39)	7 (9.72)	9 (12.5)
	Total	5 (7.58)	11 (16.67)	36 (54.55)	14 (21.21)	66 (100)	9 (12.5)	15 (20.83)	24 (33.33)	24 (33.33)	72 (100)
Cycle 2, Day 28	No pain	3 (4.69)	4 (6.25)	1 (1.56)	0	8 (12.5)	8 (11.27)	1 (1.41)	0	1 (1.41)	10 (14.08)
	Mild	2 (3.13)	6 (9.38)	18 (28.13)	2 (3.13)	28 (43.75)	1 (1.41)	11 (15.49)	7 (9.86)	3 (4.23)	22 (30.99)
	Moderate	0	1 (1.56)	13 (20.31)	8 (12.5)	22 (34.38)	0	2 (2.82)	12 (16.9)	12 (16.9)	26 (36.62)
	Severe	0	0	3 (4.69)	3 (4.69)	6 (9.38)	0	1 (1.41)	5 (7.04)	7 (9.86)	13 (18.31)
	Total	5 (7.81)	11 (17.19)	35 (54.69)	13 (20.31)	64 (100)	9 (12.68)	15 (21.13)	24 (33.8)	23 (32.39)	71 (100)
Cycle 4, Day 28	No pain	3 (4.76)	4 (6.35)	2 (3.17)	0	9 (14.29)	6 (9.09)	5 (7.58)	0	1 (1.52)	12 (18.18)
	Mild	2 (3.17)	5 (7.94)	22 (34.92)	4 (6.35)	33 (52.38)	2 (3.03)	4 (6.06)	5 (7.58)	5 (7.58)	16 (24.24)
	Moderate	0	1 (1.59)	10 (15.87)	7 (11.11)	18 (28.57)	0	4 (6.06)	15 (22.73)	7 (10.61)	26 (39.39)
	Severe	0	0	1 (1.59)	2 (3.17)	3 (4.76)	0	0	3 (4.55)	9 (13.64)	12 (18.18)
	Total	5 (7.94)	10 (15.87)	35 (55.56)	13 (20.63)	63 (100)	8 (12.12)	13 (19.7)	23 (34.85)	22 (33.33)	66 (100)

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
18.10.1: PGIS, Spikes of Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for spike pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total

N = Number of subjects in treatment group from full analysis set
PGIS = Patient Global Impression of Severity
Baseline is defined as the last result obtained prior to the start of the randomised period. Percentages are calculated using the number of subjects with a baseline value and a value
at respective post-baseline visit.
Full analysis set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
18.10.1: PGIS, Spikes of Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for spike pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total
Cycle 6, Day 28	No pain	2 (3.17)	5 (7.94)	3 (4.76)	0	10 (15.87)	7 (10.77)	5 (7.69)	0	2 (3.08)	14 (21.54)
	Mild	3 (4.76)	4 (6.35)	23 (36.51)	2 (3.17)	32 (50.79)	1 (1.54)	6 (9.23)	8 (12.31)	3 (4.62)	18 (27.69)
	Moderate	0	1 (1.59)	8 (12.7)	9 (14.29)	18 (28.57)	1 (1.54)	3 (4.62)	12 (18.46)	8 (12.31)	24 (36.92)
	Severe	0	0	1 (1.59)	2 (3.17)	3 (4.76)	0	0	2 (3.08)	7 (10.77)	9 (13.85)
	Total	5 (7.94)	10 (15.87)	35 (55.56)	13 (20.63)	63 (100)	9 (13.85)	14 (21.54)	22 (33.85)	20 (30.77)	65 (100)
Cycle 8, Day 28	No pain	4 (7.02)	4 (7.02)	4 (7.02)	0	12 (21.05)	7 (11.29)	3 (4.84)	0	1 (1.61)	11 (17.74)
	Mild	1 (1.75)	3 (5.26)	20 (35.09)	2 (3.51)	26 (45.61)	1 (1.61)	8 (12.9)	10 (16.13)	4 (6.45)	23 (37.1)
	Moderate	0	1 (1.75)	8 (14.04)	8 (14.04)	17 (29.82)	0	2 (3.23)	10 (16.13)	7 (11.29)	19 (30.65)
	Severe	0	0	1 (1.75)	1 (1.75)	2 (3.51)	0	0	2 (3.23)	7 (11.29)	9 (14.52)
	Total	5 (8.77)	8 (14.04)	33 (57.89)	11 (19.3)	57 (100)	8 (12.9)	13 (20.97)	22 (35.48)	19 (30.65)	62 (100)
Cycle 10, Day 28	No pain	2 (3.51)	6 (10.53)	1 (1.75)	1 (1.75)	10 (17.54)	6 (10.34)	4 (6.9)	2 (3.45)	2 (3.45)	14 (24.14)
	Mild	3 (5.26)	3 (5.26)	21 (36.84)	3 (5.26)	30 (52.63)	1 (1.72)	6 (10.34)	7 (12.07)	3 (5.17)	17 (29.31)
	Moderate	0	1 (1.75)	7 (12.28)	7 (12.28)	15 (26.32)	0	4 (6.9)	8 (13.79)	6 (10.34)	18 (31.03)
	Severe	0	0	1 (1.75)	1 (1.75)	2 (3.51)	0	0	3 (5.17)	6 (10.34)	9 (15.52)
	Total	5 (8.77)	10 (17.54)	30 (52.63)	12 (21.05)	57 (100)	7 (12.07)	14 (24.14)	20 (34.48)	17 (29.31)	58 (100)

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
18.10.1: PGIS, Spikes of Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for spike pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total

N = Number of subjects in treatment group from full analysis set
PGIS = Patient Global Impression of Severity
Baseline is defined as the last result obtained prior to the start of the randomised period. Percentages are calculated using the number of subjects with a baseline value and a value
at respective post-baseline visit.
Full analysis set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
18.10.1: PGIS, Spikes of Pain - Shift table by Cycle (Full Analysis Set)

		PGIS for spike pain at Baseline									
		Number (%) of subjects									
		Selumetinib 25 mg/m2 BID (N=71)					Placebo (N=74)				
Visit	PGIS	No pain	Mild	Moderate	Severe	Total	No pain	Mild	Moderate	Severe	Total
Cycle 12, Day 28	No pain	2 (3.57)	7 (12.5)	2 (3.57)	1 (1.79)	12 (21.43)	6 (10.71)	5 (8.93)	1 (1.79)	2 (3.57)	14 (25)
	Mild	3 (5.36)	1 (1.79)	17 (30.36)	4 (7.14)	25 (44.64)	1 (1.79)	6 (10.71)	7 (12.5)	1 (1.79)	15 (26.79)
	Moderate	0	1 (1.79)	10 (17.86)	6 (10.71)	17 (30.36)	0	2 (3.57)	10 (17.86)	8 (14.29)	20 (35.71)
	Severe	0	0	1 (1.79)	1 (1.79)	2 (3.57)	0	1 (1.79)	0	6 (10.71)	7 (12.5)
	Total	5 (8.93)	9 (16.07)	30 (53.57)	12 (21.43)	56 (100)	7 (12.5)	14 (25)	18 (32.14)	17 (30.36)	56 (100)

N = Number of subjects in treatment group from full analysis set
PGIS = Patient Global Impression of Severity
Baseline is defined as the last result obtained prior to the start of the randomised period. Percentages are calculated using the number of subjects with a baseline value and a value
at respective post-baseline visit.
Full analysis set consists of subjects randomised to study intervention in the study.
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2.3.4 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch

2.3.4.1 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch – Veränderung zu Baseline

Study Code: D134BC00001 Phase III PSC_U Data Cut-Off 2024-08-05

Table 8.34.1: Change from baseline in chronic PN pain medication during randomised period (Full Analysis Set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 1	Total non-missing	n	71	70
	Increased	n (%)	2 (2.8)	4 (5.7)
	Increased >=1 point	n (%)	0	0
	Increased 0.5 point	n (%)	2 (2.8)	4 (5.7)
	No change	n (%)	57 (80.3)	62 (88.6)
	Decreased	n (%)	12 (16.9)	4 (5.7)
Cycle 2	Total non-missing	n	68	70
	Increased	n (%)	2 (2.9)	7 (10.0)
	Increased >=1 point	n (%)	0	1 (1.4)
	Increased 0.5 point	n (%)	2 (2.9)	6 (8.6)
	No change	n (%)	56 (82.4)	60 (85.7)
	Decreased	n (%)	10 (14.7)	3 (4.3)

PN = Plexiform Neurofibroma; WHO = World Health Organization; n = Number of subjects per category
N = Number of subjects in treatment group from full analysis set
Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)).
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic lad der score
as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5).
Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirem ent for
increase.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_chg_painmed.sas Executed: 10NOV2025 18:23:39

Study Code: D134BC00001 Phase III PSC_U Data Cut-Off 2024-08-05

Table 8.34.1: Change from baseline in chronic PN pain medication during randomised period (Full Analysis Set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 3	Total non-missing	n	67	69
	Increased	n (%)	3 (4.5)	7 (10.1)
	Increased >=1 point	n (%)	1 (1.5)	1 (1.4)
	Increased 0.5 point	n (%)	2 (3.0)	6 (8.7)
	No change	n (%)	46 (68.7)	54 (78.3)
	Decreased	n (%)	18 (26.9)	8 (11.6)
Cycle 4	Total non-missing	n	65	69
	Increased	n (%)	1 (1.5)	5 (7.2)
	Increased >=1 point	n (%)	0	1 (1.4)
	Increased 0.5 point	n (%)	1 (1.5)	4 (5.8)
	No change	n (%)	48 (73.8)	56 (81.2)
	Decreased	n (%)	16 (24.6)	8 (11.6)

PN = Plexiform Neurofibroma; WHO = World Health Organization; n = Number of subjects per category
N = Number of subjects in treatment group from full analysis set
Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)).
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic lad der score
as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5).
Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirem ent for
increase.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III PSC_U Data Cut-Off 2024-08-05

Table 8.34.1: Change from baseline in chronic PN pain medication during randomised period (Full Analysis Set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 5	Total non-missing	n	65	67
	Increased	n (%)	1 (1.5)	4 (6.0)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	1 (1.5)	3 (4.5)
	No change	n (%)	44 (67.7)	54 (80.6)
	Decreased	n (%)	20 (30.8)	9 (13.4)
Cycle 6	Total non-missing	n	65	67
	Increased	n (%)	1 (1.5)	6 (9.0)
	Increased >=1 point	n (%)	0	2 (3.0)
	Increased 0.5 point	n (%)	1 (1.5)	4 (6.0)
	No change	n (%)	47 (72.3)	56 (83.6)
	Decreased	n (%)	17 (26.2)	5 (7.5)

PN = Plexiform Neurofibroma; WHO = World Health Organization; n = Number of subjects per category
N = Number of subjects in treatment group from full analysis set
Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)).
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic lad der score
as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5).
Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirem ent for
increase.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III PSC_U Data Cut-Off 2024-08-05

Table 8.34.1: Change from baseline in chronic PN pain medication during randomised period (Full Analysis Set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 7	Total non-missing	n	65	66
	Increased	n (%)	0	7 (10.6)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	0	6 (9.1)
	No change	n (%)	48 (73.8)	51 (77.3)
	Decreased	n (%)	17 (26.2)	8 (12.1)
Cycle 8	Total non-missing	n	64	66
	Increased	n (%)	2 (3.1)	8 (12.1)
	Increased >=1 point	n (%)	1 (1.6)	2 (3.0)
	Increased 0.5 point	n (%)	1 (1.6)	6 (9.1)
	No change	n (%)	48 (75.0)	52 (78.8)
	Decreased	n (%)	14 (21.9)	6 (9.1)

PN = Plexiform Neurofibroma; WHO = World Health Organization; n = Number of subjects per category
N = Number of subjects in treatment group from full analysis set
Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)).
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic lad der score
as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5).
Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirem ent for
increase.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_chg_painmed.sas Executed: 10NOV2025 18:23:39

Study Code: D134BC00001 Phase III PSC_U Data Cut-Off 2024-08-05

Table 8.34.1: Change from baseline in chronic PN pain medication during randomised period (Full Analysis Set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 9	Total non-missing	n	62	62
	Increased	n (%)	1 (1.6)	6 (9.7)
	Increased >=1 point	n (%)	0	1 (1.6)
	Increased 0.5 point	n (%)	1 (1.6)	5 (8.1)
	No change	n (%)	44 (71.0)	48 (77.4)
	Decreased	n (%)	17 (27.4)	8 (12.9)
Cycle 10	Total non-missing	n	61	63
	Increased	n (%)	1 (1.6)	7 (11.1)
	Increased >=1 point	n (%)	0	1 (1.6)
	Increased 0.5 point	n (%)	1 (1.6)	6 (9.5)
	No change	n (%)	42 (68.9)	47 (74.6)
	Decreased	n (%)	18 (29.5)	9 (14.3)

PN = Plexiform Neurofibroma; WHO = World Health Organization; n = Number of subjects per category
N = Number of subjects in treatment group from full analysis set
Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)).
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic lad der score
as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5).
Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirem ent for
increase.
Full Analysis Set consists of subjects randomised to study intervention in the study.
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Study Code: D134BC00001 Phase III PSC_U Data Cut-Off 2024-08-05

Table 8.34.1: Change from baseline in chronic PN pain medication during randomised period (Full Analysis Set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 11	Total non-missing	n	59	64
	Increased	n (%)	2 (3.4)	6 (9.4)
	Increased >=1 point	n (%)	0	1 (1.6)
	Increased 0.5 point	n (%)	2 (3.4)	5 (7.8)
	No change	n (%)	40 (67.8)	49 (76.6)
	Decreased	n (%)	17 (28.8)	9 (14.1)
Cycle 12	Total non-missing	n	57	61
	Increased	n (%)	2 (3.5)	5 (8.2)
	Increased >=1 point	n (%)	0	1 (1.6)
	Increased 0.5 point	n (%)	2 (3.5)	4 (6.6)
	No change	n (%)	39 (68.4)	46 (75.4)
	Decreased	n (%)	16 (28.1)	10 (16.4)

PN = Plexiform Neurofibroma; WHO = World Health Organization; n = Number of subjects per category
N = Number of subjects in treatment group from full analysis set
Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)).
Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e. Total non-missing).
An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic lad der score
as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5).
Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirem ent for
increase.
Full Analysis Set consists of subjects randomised to study intervention in the study.
Program: t_chg_painmed.sas Executed: 10NOV2025 18:23:39

2.3.4.2 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch – Werte im Studienverlauf

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.16.1: Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full Analysis Set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Baseline	Total non-missing	n	71	72
	0-No Analgesia	n (%)	33 (46.48)	37 (51.39)
	1-Non-opioids	n (%)	15 (21.13)	11 (15.28)
	2-Neuropathic/other non-typical pain medications	n (%)	18 (25.35)	12 (16.67)
	3-Weak opioids	n (%)	2 (2.82)	3 (4.17)
	4-Strong opioids	n (%)	3 (4.23)	9 (12.50)
Cycle 1	Total non-missing	n	71	70
	0-No Analgesia	n (%)	43 (60.56)	40 (57.14)
	1-Non-opioids	n (%)	11 (15.49)	7 (10.00)
	2-Neuropathic/other non-typical pain medications	n (%)	12 (16.90)	11 (15.71)
	3-Weak opioids	n (%)	2 (2.82)	3 (4.29)
	4-Strong opioids	n (%)	3 (4.23)	9 (12.86)
Cycle 2	Total non-missing	n	68	70
	0-No Analgesia	n (%)	42 (61.76)	36 (51.43)
	1-Non-opioids	n (%)	9 (13.24)	10 (14.29)
	2-Neuropathic/other non-typical pain medications	n (%)	12 (17.65)	10 (14.29)
	3-Weak opioids	n (%)	2 (2.94)	4 (5.71)
	4-Strong opioids	n (%)	3 (4.41)	10 (14.29)

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.16.1: Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full Analysis Set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)

Any chronic PN pain medication recorded in the daily e-
Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the
Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding
visit (i.e., Total non-missing).
n = Number of subjects per category; N = Number of subjects in treatment group; PN = Plexiform Neurofibroma; WHO = World Health Organization.
WHODrug Global B3-format Sep 2023.
Full analysis set - subjects randomised to study intervention.
Program: t_pn_ladder.sas Executed: 11NOV2025 14:01:19

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.16.1: Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full Analysis Set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 3	Total non-missing	n	67	69
	0-No Analgesia	n (%)	46 (68.66)	42 (60.87)
	1-Non-opioids	n (%)	6 (8.96)	6 (8.70)
	2-Neuropathic/other non-typical pain medications	n (%)	11 (16.42)	10 (14.49)
	3-Weak opioids	n (%)	2 (2.99)	2 (2.90)
	4-Strong opioids	n (%)	2 (2.99)	9 (13.04)
Cycle 4	Total non-missing	n	65	69
	0-No Analgesia	n (%)	44 (67.69)	42 (60.87)
	1-Non-opioids	n (%)	6 (9.23)	6 (8.70)
	2-Neuropathic/other non-typical pain medications	n (%)	11 (16.92)	10 (14.49)
	3-Weak opioids	n (%)	2 (3.08)	2 (2.90)
	4-Strong opioids	n (%)	2 (3.08)	9 (13.04)
Cycle 5	Total non-missing	n	65	67
	0-No Analgesia	n (%)	49 (75.38)	42 (62.69)
	1-Non-opioids	n (%)	5 (7.69)	6 (8.96)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (12.31)	8 (11.94)
	3-Weak opioids	n (%)	2 (3.08)	3 (4.48)
	4-Strong opioids	n (%)	1 (1.54)	8 (11.94)

Any chronic PN pain medication recorded in the daily e-
Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the
Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding
visit (i.e., Total non-missing).
n = Number of subjects per category; N = Number of subjects in treatment group; PN = Plexiform Neurofibroma; WHO = World Health Organization.
WHODrug Global B3-format Sep 2023.
Full analysis set - subjects randomised to study intervention.
Program: t_pn_ladder.sas Executed: 11NOV2025 14:01:19

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.16.1: Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full Analysis Set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 6	Total non-missing	n	65	67
	0-No Analgesia	n (%)	45 (69.23)	38 (56.72)
	1-Non-opioids	n (%)	5 (7.69)	7 (10.45)
	2-Neuropathic/other non-typical pain medications	n (%)	11 (16.92)	10 (14.93)
	3-Weak opioids	n (%)	2 (3.08)	4 (5.97)
	4-Strong opioids	n (%)	2 (3.08)	8 (11.94)
Cycle 7	Total non-missing	n	65	66
	0-No Analgesia	n (%)	44 (67.69)	41 (62.12)
	1-Non-opioids	n (%)	7 (10.77)	5 (7.58)
	2-Neuropathic/other non-typical pain medications	n (%)	9 (13.85)	10 (15.15)
	3-Weak opioids	n (%)	3 (4.62)	3 (4.55)
	4-Strong opioids	n (%)	2 (3.08)	7 (10.61)
Cycle 8	Total non-missing	n	64	66
	0-No Analgesia	n (%)	40 (62.50)	39 (59.09)
	1-Non-opioids	n (%)	5 (7.81)	7 (10.61)
	2-Neuropathic/other non-typical pain medications	n (%)	12 (18.75)	11 (16.67)
	3-Weak opioids	n (%)	5 (7.81)	1 (1.52)
	4-Strong opioids	n (%)	2 (3.13)	8 (12.12)

Any chronic PN pain medication recorded in the daily e-
Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the
Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding
visit (i.e., Total non-missing).
n = Number of subjects per category; N = Number of subjects in treatment group; PN = Plexiform Neurofibroma; WHO = World Health Organization.
WHODrug Global B3-format Sep 2023.
Full analysis set - subjects randomised to study intervention.
Program: t_pn_ladder.sas Executed: 11NOV2025 14:01:19

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.16.1: Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full Analysis Set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 9	Total non-missing	n	62	62
	0-No Analgesia	n (%)	42 (67.74)	41 (66.13)
	1-Non-opioids	n (%)	6 (9.68)	4 (6.45)
	2-Neuropathic/other non-typical pain medications	n (%)	10 (16.13)	9 (14.52)
	3-Weak opioids	n (%)	3 (4.84)	1 (1.61)
	4-Strong opioids	n (%)	1 (1.61)	7 (11.29)
Cycle 10	Total non-missing	n	61	63
	0-No Analgesia	n (%)	44 (72.13)	40 (63.49)
	1-Non-opioids	n (%)	6 (9.84)	3 (4.76)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (13.11)	10 (15.87)
	3-Weak opioids	n (%)	1 (1.64)	2 (3.17)
	4-Strong opioids	n (%)	2 (3.28)	8 (12.70)
Cycle 11	Total non-missing	n	59	64
	0-No Analgesia	n (%)	43 (72.88)	40 (62.50)
	1-Non-opioids	n (%)	5 (8.47)	5 (7.81)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (13.56)	9 (14.06)
	3-Weak opioids	n (%)	1 (1.69)	3 (4.69)
	4-Strong opioids	n (%)	2 (3.39)	7 (10.94)

Any chronic PN pain medication recorded in the daily e-
Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the
Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding
visit (i.e., Total non-missing).
n = Number of subjects per category; N = Number of subjects in treatment group; PN = Plexiform Neurofibroma; WHO = World Health Organization.
WHODrug Global B3-format Sep 2023.
Full analysis set - subjects randomised to study intervention.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 8.16.1: Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full Analysis Set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)
Cycle 12	Total non-missing	n	57	61
	0-No Analgesia	n (%)	41 (71.93)	42 (68.85)
	1-Non-opioids	n (%)	6 (10.53)	3 (4.92)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (14.04)	7 (11.48)
	3-Weak opioids	n (%)	0	2 (3.28)
	4-Strong opioids	n (%)	2 (3.51)	7 (11.48)

Any chronic PN pain medication recorded in the daily e-
Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the
Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding
visit (i.e., Total non-missing).
n = Number of subjects per category; N = Number of subjects in treatment group; PN = Plexiform Neurofibroma; WHO = World Health Organization.
WHODrug Global B3-format Sep 2023.
Full analysis set - subjects randomised to study intervention.
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2.3.5 PII-pNF – FAS

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 15.1.1: PII-pNF: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	70 (98.59)	2.64 (1.60)							
	Placebo, N=74	72 (97.30)	2.42 (1.68)							
Cycle 1, Day 28	Selumetinib 25 mg/m2 BID, N=71	67 (94.37)	2.11 (1.50)	66 (92.96)	-0.50 (0.12)	(-0.73, -0.26)	0.14	(-0.14, 0.42)	0.331	
	Placebo, N=74	74 (100)	1.78 (1.43)	72 (97.30)	-0.64 (0.12)	(-0.88, -0.40)				
Cycle 2, Day 28	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	1.84 (1.54)	64 (90.14)	-0.79 (0.14)	(-1.07, -0.50)	-0.18	(-0.54, 0.17)	0.312	
	Placebo, N=74	73 (98.65)	1.77 (1.52)	71 (95.95)	-0.60 (0.14)	(-0.88, -0.32)				
Cycle 4, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	1.72 (1.38)	63 (88.73)	-0.93 (0.14)	(-1.20, -0.66)	-0.30	(-0.64, 0.04)	0.080	
	Placebo, N=74	68 (91.89)	1.76 (1.47)	66 (89.19)	-0.63 (0.14)	(-0.90, -0.36)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 15.1.1: PII-pNF: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PII-pNF= Pain interference index – plexiform neurofibroma.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 15.1.1: PII-pNF: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 6, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	1.79 (1.45)	63 (88.73)	-0.87 (0.15)	(-1.16, -0.57)	-0.16	(-0.53, 0.21)	0.389	
	Placebo, N=74	67 (90.54)	1.66 (1.42)	65 (87.84)	-0.70 (0.15)	(-0.99, -0.42)				
Cycle 8, Day 28	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	1.74 (1.48)	57 (80.28)	-0.88 (0.16)	(-1.19, -0.56)	-0.37	(-0.78, 0.03)	0.070	
	Placebo, N=74	64 (86.49)	1.74 (1.48)	62 (83.78)	-0.50 (0.16)	(-0.81, -0.19)				
Cycle 10, Day 28	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	1.68 (1.50)	58 (81.69)	-1.01 (0.15)	(-1.31, -0.70)	-0.50	(-0.88, -0.11)	0.012	-0.43 (-0.80, -0.06)
	Placebo, N=74	63 (85.14)	1.68 (1.53)	61 (82.43)	-0.51 (0.15)	(-0.81, -0.21)				
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	1.71 (1.53)	57 (80.28)	-0.95 (0.16)	(-1.27, -0.63)	-0.48	(-0.90, -0.07)	0.023	-0.39 (-0.77, -0.02)
	Placebo, N=74	61 (82.43)	1.72 (1.49)	59 (79.73)	-0.47 (0.16)	(-0.78, -0.15)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 15.1.1: PII-pNF: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PII-pNF= Pain interference index – plexiform neurofibroma.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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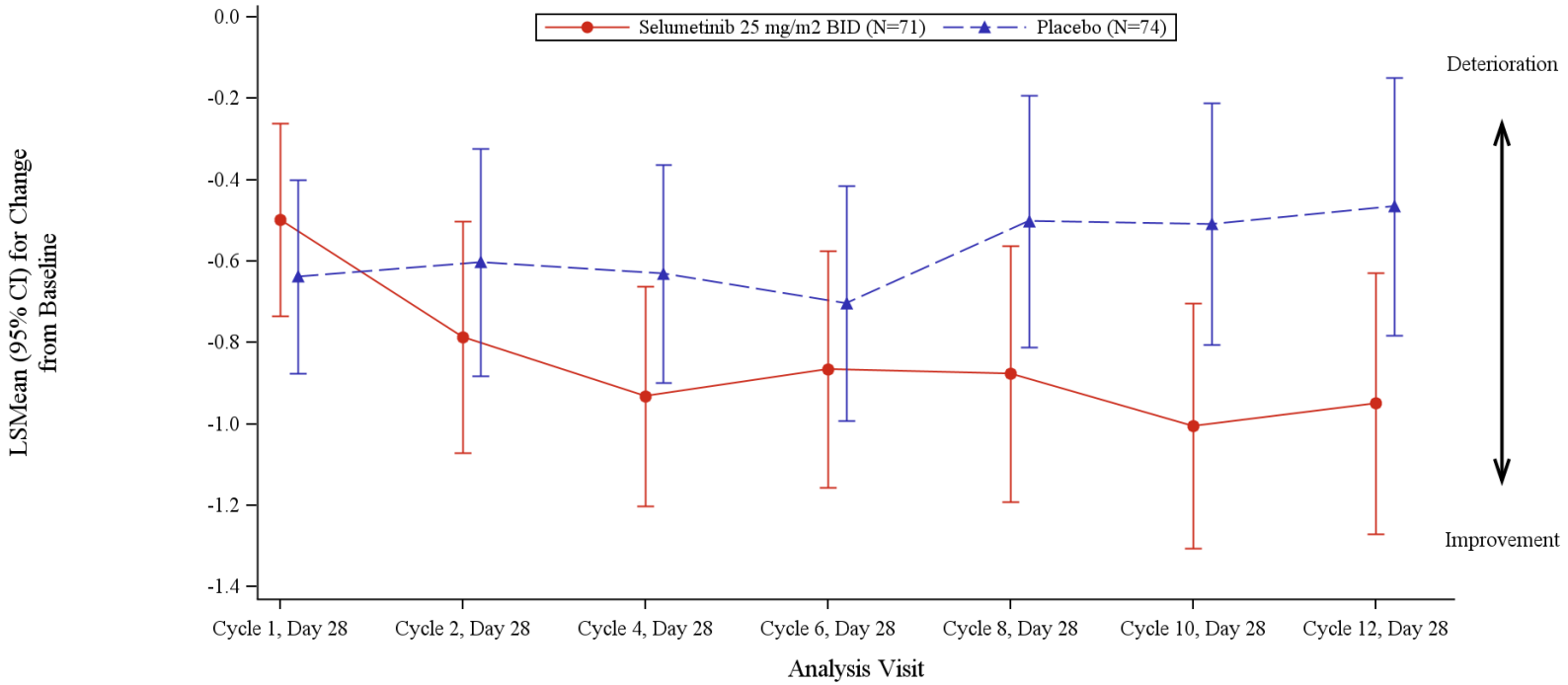
Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 15.1.1: PII-pNF: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	68 (95.77)	1.80 (1.48)	67 (94.37)	-0.84 (0.12)	(-1.09, -0.60)	-0.27	(-0.57, 0.03)	0.081	
	Placebo, N=74	74 (100)	1.73 (1.47)	72 (97.30)	-0.58 (0.12)	(-0.82, -0.33)				

PII-pNF= Pain interference index – plexiform neurofibroma.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:30:05

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Figure 14.2.12.5 LS mean change from baseline in PII-pNF pain interference total scores over the randomised period (Full analysis set)



Number of subjects							
Selumetinib 25 mg/m2 BID	66	64	63	63	57	58	57
Placebo	72	71	66	65	62	61	59

Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment groupcycle, baseline scorecycle. Unstructured covariance matrix is used. LS Means on the treatment groupcycle interaction are plotted. Error bars represent 95% CIs. CI Confidence Interval. LS Least Square. N Number of subjects in treatment group. PII-pNF Pain interference index – plexiform neurofibroma. Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off. Full analysis set - subjects randomised to study intervention.

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2.3.6 EQ-5D VAS

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 13.1.1: EQ-VAS: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	70 (98.59)	63.54 (19.06)							
	Placebo, N=74	72 (97.30)	62.10 (21.18)							
Cycle 2, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	67.97 (19.35)	63 (88.73)	5.30 (2.07)	(1.21, 9.40)	-1.12	(-6.26, 4.02)	0.668	
	Placebo, N=74	73 (98.65)	67.93 (19.04)	71 (95.95)	6.42 (1.95)	(2.57, 10.27)				
Cycle 4, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	68.22 (20.36)	63 (88.73)	6.43 (2.25)	(1.98, 10.89)	0.66	(-5.09, 6.42)	0.821	
	Placebo, N=74	68 (91.89)	67.18 (19.63)	66 (89.19)	5.77 (2.16)	(1.50, 10.05)				
Cycle 8, Day 28	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	66.64 (20.41)	58 (81.69)	4.68 (2.30)	(0.12, 9.24)	1.13	(-4.75, 7.02)	0.704	
	Placebo, N=74	65 (87.84)	65.11 (20.56)	63 (85.14)	3.55 (2.18)	(-0.78, 7.87)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 13.1.1: EQ-VAS: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

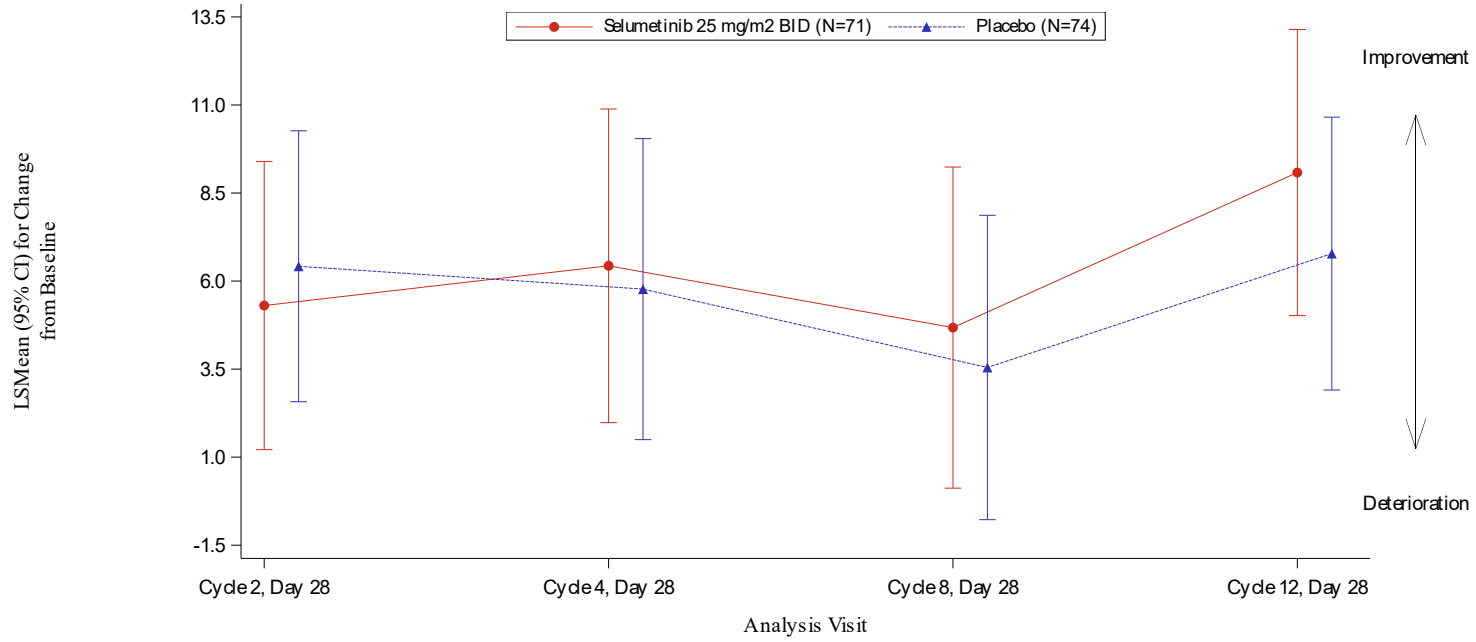
EQ-VAS= EuroQol visual analogue scale
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:29:59

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 13.1.1: EQ-VAS: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	71.24 (18.32)	57 (80.28)	9.08 (2.05)	(5.02, 13.14)	2.30	(-2.88, 7.48)	0.381	
	Placebo, N=74	61 (82.43)	69.18 (18.23)	59 (79.73)	6.78 (1.96)	(2.91, 10.65)				
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	68.49 (19.59)	64 (90.14)	6.37 (1.70)	(3.01, 9.74)	0.74	(-3.30, 4.79)	0.716	
	Placebo, N=74	73 (98.65)	67.34 (19.34)	71 (95.95)	5.63 (1.60)	(2.47, 8.79)				

EQ-VAS= EuroQol visual analogue scale
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:29:59

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-0
Figure 13.1.1.3: EQ-VAS: LS Mean change from baseline (Full Analysis Set)



Number of subjects				
Selumetinib 25 mg/m2 BID	63	63	58	57
Placebo	71	66	63	59

EQ-VAS= EuroQol visual analogue scale
N = Number of subjects in treatment group, LS = Least Square, CI = Confidence Interval
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical
region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means on the treatement group*cycle interaction are plotted. Error bars represent 95% CIs.
Full analysis set - subjects randomised to study intervention
Program: f_chg_sum.sas Executed: 11APR2025 14:40:58

2.3.7 PROMIS

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 16.1.1: PROMIS, T-score: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	70 (98.59)	41.45 (7.97)							
	Placebo, N=74	72 (97.30)	41.95 (9.35)							
Cycle 2, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	42.65 (6.66)	63 (88.73)	1.15 (0.82)	(-0.47, 2.76)	-2.27	(-4.24, -0.30)	0.025	-0.34 (-0.69, 0.00)
	Placebo, N=74	73 (98.65)	45.61 (10.03)	71 (95.95)	3.41 (0.79)	(1.86, 4.96)				
Cycle 4, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	43.32 (6.68)	63 (88.73)	1.98 (0.81)	(0.38, 3.58)	-0.77	(-2.73, 1.20)	0.441	
	Placebo, N=74	68 (91.89)	44.98 (10.43)	66 (89.19)	2.75 (0.79)	(1.19, 4.30)				
Cycle 8, Day 28	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	44.26 (7.81)	58 (81.69)	3.16 (0.88)	(1.42, 4.90)	1.09	(-1.09, 3.27)	0.324	
	Placebo, N=74	65 (87.84)	44.97 (10.60)	63 (85.14)	2.07 (0.85)	(0.39, 3.75)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 16.1.1: PROMIS, T-score: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

PROMIS= Patient-Reported Outcomes Measurement Information System. Analysis is using T-Score.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:30:41

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 16.1.1: PROMIS, T-score: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	43.57 (8.35)	57 (80.28)	2.30 (0.90)	(0.53, 4.07)	-0.62	(-2.86, 1.63)	0.588	
	Placebo, N=74	61 (82.43)	45.70 (10.80)	59 (79.73)	2.92 (0.87)	(1.19, 4.64)				
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	43.43 (7.35)	64 (90.14)	2.15 (0.75)	(0.67, 3.62)	-0.64	(-2.40, 1.12)	0.474	
	Placebo, N=74	73 (98.65)	45.31 (10.40)	71 (95.95)	2.79 (0.72)	(1.36, 4.22)				

PROMIS= Patient-Reported Outcomes Measurement Information System. Analysis is using T-Score.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
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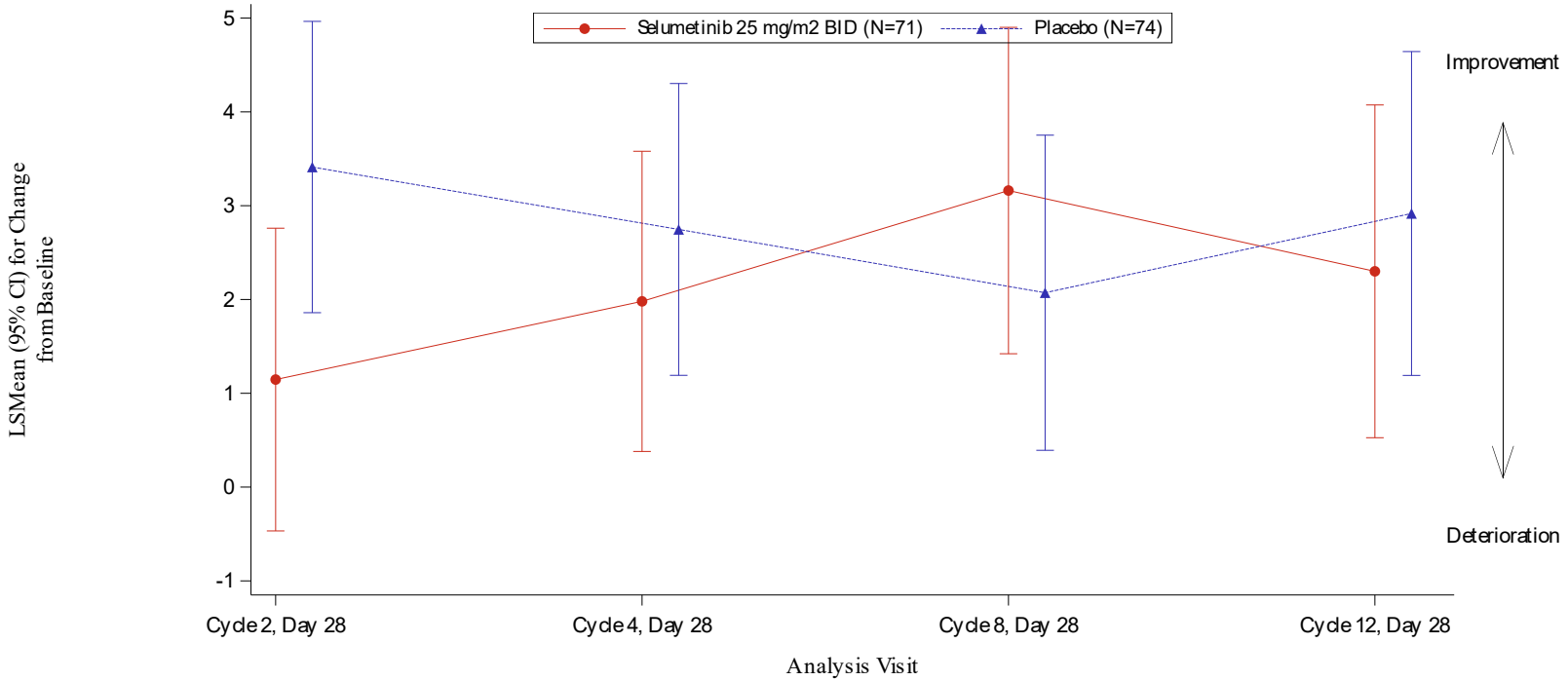
Study Code: D134BC00001 Phase III Page 1 of 1
PSC_U Data Cut-Off 2024-08-05
Figure 16.1.1.3: PROMIS, T-score: LS Mean change from baseline (Full Analysis Set)



Number of subjects				
Selumetinib 25 mg/m2 BID	63	63	58	57
Placebo	71	66	63	59

PROMIS= Patient-Reported Outcomes Measurement Information System. Analysis is using T-Score.
N = Number of subjects in treatment group, LS = Least Square, CI = Confidence Interval
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical
region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means on the treatement group*cycle interaction are plotted. Error bars represent 95% CIs.
Full analysis set - subjects randomised to study intervention
Program: f_chg_sum.sas Executed: 11APR2025 14:41:21

2.3.8 PlexiQoL

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 20.1.1: PlexiQoL: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	70 (98.59)	9.34 (4.73)							
	Placebo, N=74	72 (97.30)	8.06 (4.10)							
Cycle 2, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	8.31 (5.03)	63 (88.73)	-0.75 (0.42)	(-1.57, 0.08)	-0.02	(-1.06, 1.01)	0.964	
	Placebo, N=74	73 (98.65)	7.11 (4.36)	71 (95.95)	-0.72 (0.40)	(-1.52, 0.07)				
Cycle 4, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	8.56 (5.02)	63 (88.73)	-0.67 (0.40)	(-1.47, 0.13)	0.20	(-0.80, 1.21)	0.691	
	Placebo, N=74	68 (91.89)	6.97 (4.47)	66 (89.19)	-0.87 (0.39)	(-1.65, -0.09)				
Cycle 8, Day 28	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	8.47 (4.83)	58 (81.69)	-0.84 (0.45)	(-1.74, 0.05)	-0.24	(-1.40, 0.92)	0.683	
	Placebo, N=74	65 (87.84)	7.14 (4.94)	63 (85.14)	-0.61 (0.44)	(-1.47, 0.26)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 20.1.1: PlexiQoL: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

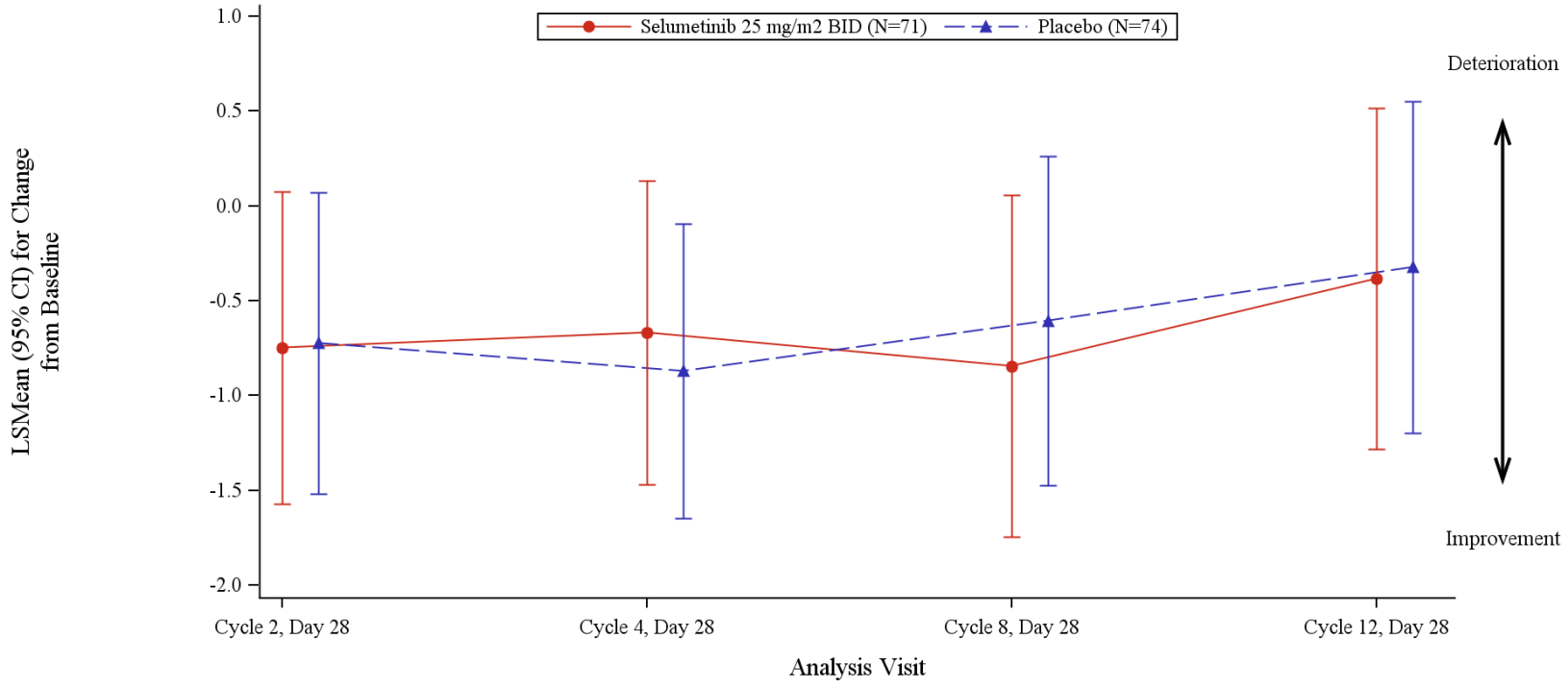
PlexiQoL= Plexiform Neurofibroma Quality of Life scale.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:30:03

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 20.1.1: PlexiQoL: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	8.79 (5.12)	57 (80.28)	-0.38 (0.45)	(-1.28, 0.52)	-0.06	(-1.23, 1.11)	0.918	
	Placebo, N=74	61 (82.43)	7.44 (4.86)	59 (79.73)	-0.32 (0.44)	(-1.20, 0.55)				
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	8.53 (4.97)	64 (90.14)	-0.66 (0.38)	(-1.41, 0.09)	-0.03	(-0.96, 0.90)	0.949	
	Placebo, N=74	73 (98.65)	7.16 (4.62)	71 (95.95)	-0.63 (0.37)	(-1.36, 0.10)				

PlexiQoL= Plexiform Neurofibroma Quality of Life scale.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:30:03

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Figure 14.2.3.2.1 LS mean change from baseline in PlexiQoL total scores over the randomised period (Full analysis set)



Number of subjects				
Selumetinib 25 mg/m2 BID	63	63	58	57
Placebo	71	66	63	59

Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment groupcycle, baseline scorecycle. Unstructured covariance matrix is used. LS Means on the treatment groupcycle interaction are plotted. Error bars represent 95% CIs. CI Confidence Interval. LS Least Square. N Number of subjects in treatment group. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Randomised period - first dose date until earliest; of last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off. Full analysis set - subjects randomised to study intervention.

Program: S:\AZ\Selumetinib\KOMET\PSC_U\Prog\Output\eff361.sas Executed : 2024-11-12T155540

2.3.9 PedsQL NF1

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 19.1.1: PedsQL: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Baseline	Selumetinib 25 mg/m2 BID, N=71	71 (100)	59.98 (25.22)							
	Placebo, N=74	72 (97.30)	61.11 (28.18)							
Cycle 2, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	62.50 (25.97)	64 (90.14)	3.67 (2.50)	(-1.28, 8.62)	-3.00	(-9.09, 3.09)	0.332	
	Placebo, N=74	73 (98.65)	66.55 (23.75)	71 (95.95)	6.67 (2.42)	(1.88, 11.45)				
Cycle 4, Day 28	Selumetinib 25 mg/m2 BID, N=71	64 (90.14)	64.19 (23.46)	64 (90.14)	5.34 (2.44)	(0.52, 10.16)	-2.22	(-8.15, 3.70)	0.459	
	Placebo, N=74	68 (91.89)	67.89 (22.91)	66 (89.19)	7.56 (2.38)	(2.86, 12.27)				
Cycle 8, Day 28	Selumetinib 25 mg/m2 BID, N=71	59 (83.10)	63.42 (24.90)	59 (83.10)	5.42 (2.51)	(0.45, 10.39)	-1.93	(-8.07, 4.21)	0.536	
	Placebo, N=74	65 (87.84)	68.21 (24.78)	63 (85.14)	7.35 (2.44)	(2.53, 12.17)				

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 19.1.1: PedsQL: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)

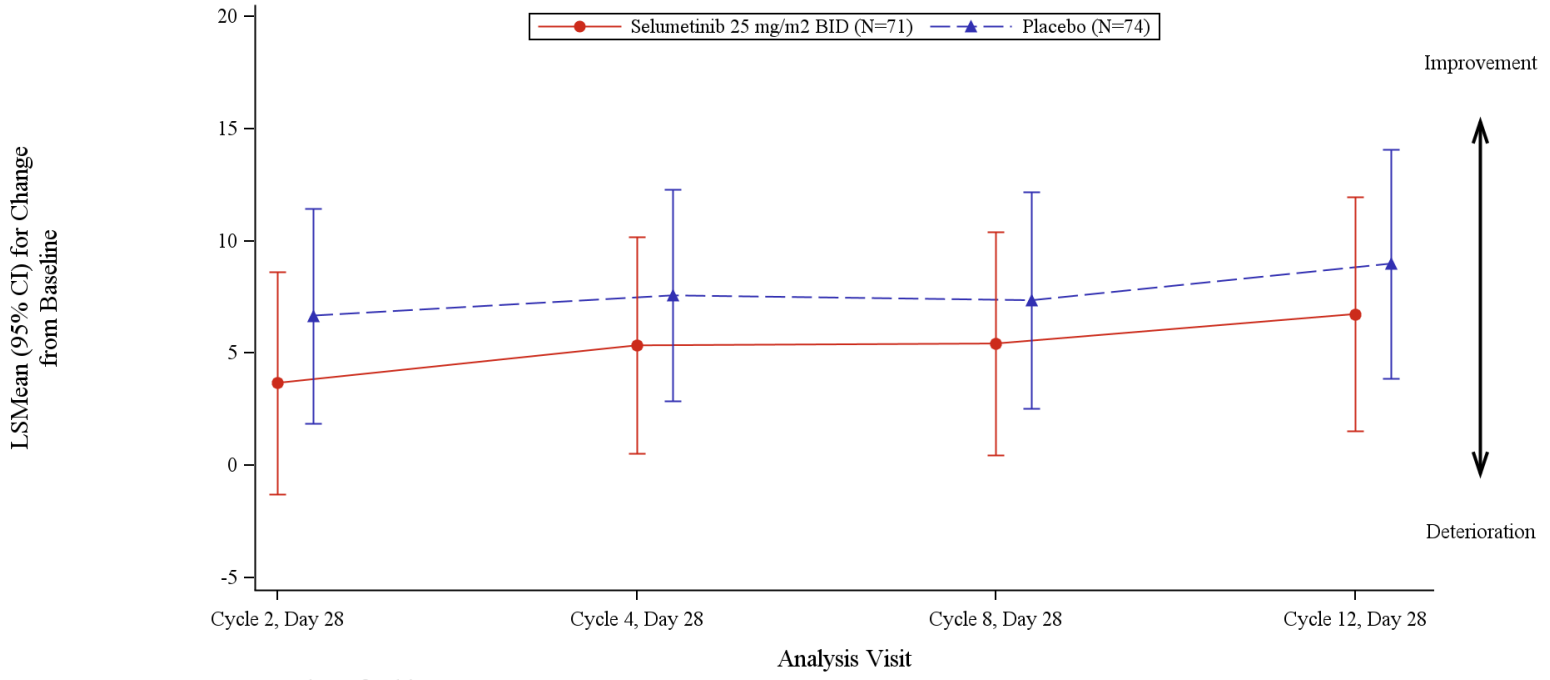
PedsQL NF1= Paediatric Quality of Life Inventory Neurofibromatosis type 1.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:30:01

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 19.1.1: PedsQL: Change from baseline, absolute values and change (Full Analysis Set)

		Actual value		Change from baseline			Comparison of Treatment Groups			
Timepoint	Treatment	n (%)	Mean (SD)	n1 (%)	LS Mean (SE)	(95% CI)	LS Mean difference	(95% CI)	p-value	SMD Hedges' g^ (95% CI)
Cycle 12, Day 28	Selumetinib 25 mg/m2 BID, N=71	58 (81.69)	65.23 (26.77)	58 (81.69)	6.73 (2.63)	(1.53, 11.94)	-2.25	(-8.82, 4.32)	0.500	
	Placebo, N=74	61 (82.43)	69.40 (24.66)	59 (79.73)	8.98 (2.58)	(3.88, 14.08)				
Over Rando-mised Period	Selumetinib 25 mg/m2 BID, N=71	65 (91.55)	63.81 (25.14)	65 (91.55)	5.29 (2.23)	(0.88, 9.70)	-2.35	(-7.59, 2.89)	0.377	
	Placebo, N=74	73 (98.65)	67.95 (23.89)	71 (95.95)	7.64 (2.16)	(3.36, 11.92)				

PedsQL NF1= Paediatric Quality of Life Inventory Neurofibromatosis type 1.
N = Number of subjects in treatment group, n = Number of subjects with non-missing result at specified visit, n1 = Number of subjects with non-missing change from baseline at
specified visit, SD = Standard deviation, SE = Standard error, CI = Confidence Interval, LS = Least Square, SMD = Standardized Mean Difference
Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date.
A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement.
Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score,
geographical region, treatment group*cycle, baseline score*cycle. Unstructured covariance matrix is used. LS means and LS mean differences were estimated on the treatment
group*cycle interaction. P-values are nominal and reflect the 2-sided Type 3 test with alpha=0.05 level.
^Hedges G is calculated when p-value is < 0.05
Full analysis set - subjects randomised to study intervention
Program: t_chg_sum.sas Executed: 11JUL2025 11:30:01

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Figure 14.2.14.5 LS mean change from baseline in PedsQL skin sensations scores over the randomised period (Full analysis set)



Number of subjects				
Selumetinib 25 mg/m2 BID	64	64	59	58
Placebo	71	66	63	59

Analysis is based on a Mixed Model for Repeated Measures (MMRM) for Change from Baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment groupcycle, baseline scorecycle. Unstructured covariance matrix is used. LS Means on the treatment groupcycle interaction are plotted. Error bars represent 95% CIs. CI Confidence Interval. LS Least Square. N Number of subjects in treatment group. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Randomised period - first dose date until earliest of; last dose of Cycle 12, crossover, day prior to start of subsequent therapy, or data cut-off. Full analysis set - subjects randomised to study intervention.

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2.4 Begleitmedikation in der Studie KOMET

2.4.1 Erlaubte Begleitmedikation in der Studie KOMET

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
Number of subjects with allowed concomitant medication	71 (100)	69 (93.2)	140 (96.6)
PROPIONIC ACID DERIVATIVES	37 (52.1)	32 (43.2)	69 (47.6)
Ibuprofen	23 (32.4)	20 (27.0)	43 (29.7)
Loxoprofen sodium dihydrate	5 (7.0)	3 (4.1)	8 (5.5)
Ketoprofen	3 (4.2)	2 (2.7)	5 (3.4)
Loxoprofen	1 (1.4)	3 (4.1)	4 (2.8)
Naproxen	4 (5.6)	0	4 (2.8)
Naproxen sodium	1 (1.4)	2 (2.7)	3 (2.1)
Dexketoprofen	1 (1.4)	1 (1.4)	2 (1.4)
Loxoprofen sodium	0	2 (2.7)	2 (1.4)
Dexketoprofen trometamol	1 (1.4)	0	1 (0.7)

Flurbiprofen	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,
or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ANILIDES	27 (38.0)	26 (35.1)	53 (36.6)
Paracetamol	24 (33.8)	20 (27.0)	44 (30.3)
Amantadine hydrochloride;caffeine;chlorphenamine maleate;cow bezoar;paracetamol	1 (1.4)	1 (1.4)	2 (1.4)
Chlorphenamine maleate;dextromethorphan hydrobromide;paracetamol;pseudoephedrine hydrochloride	0	2 (2.7)	2 (1.4)
Acetylsalicylic acid;caffeine;paracetamol	0	1 (1.4)	1 (0.7)
Aluminium hydroxide;apronal;caffeine;ibuprofen;paracetamol	1 (1.4)	0	1 (0.7)
Ascorbic acid;paracetamol	1 (1.4)	0	1 (0.7)
Ascorbic acid;paracetamol;pheniramine maleate	1 (1.4)	0	1 (0.7)
Caffeine;chlorphenamine maleate;cow bezoar;paracetamol	0	1 (1.4)	1 (0.7)
Caffeine;paracetamol;promethazine methylene disalicylate;salicylamide	0	1 (1.4)	1 (0.7)
Chlorphenamine maleate;paracetamol	0	1 (1.4)	1 (0.7)
Dextromethorphan hydrobromide;paracetamol;pseudoephedrine hydrochloride	0	1 (1.4)	1 (0.7)
Paracetamol;pseudoephedrine hydrochloride	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date

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until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,
or data cut-off.
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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
GABAPENTINOIDS	16 (22.5)	23 (31.1)	39 (26.9)
Pregabalin	10 (14.1)	13 (17.6)	23 (15.9)
Gabapentin	6 (8.5)	7 (9.5)	13 (9.0)
Mirogabalin besilate	0	4 (5.4)	4 (2.8)
ANTIINFECTIVES FOR TREATMENT OF ACNE	30 (42.3)	3 (4.1)	33 (22.8)
Clindamycin	13 (18.3)	1 (1.4)	14 (9.7)
Clindamycin phosphate	10 (14.1)	2 (2.7)	12 (8.3)
Nadifloxacin	3 (4.2)	0	3 (2.1)
Ozenoxacin	3 (4.2)	0	3 (2.1)
Erythromycin	2 (2.8)	0	2 (1.4)
Clindamycin hydrochloride	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
TETRACYCLINES	29 (40.8)	3 (4.1)	32 (22.1)
Doxycycline	22 (31.0)	3 (4.1)	25 (17.2)
Minocycline	3 (4.2)	0	3 (2.1)
Doxycycline hyclate	2 (2.8)	0	2 (1.4)
Minocycline hydrochloride	2 (2.8)	0	2 (1.4)
Lymecycline	1 (1.4)	0	1 (0.7)
VITAMIN D AND ANALOGUES	11 (15.5)	13 (17.6)	24 (16.6)
Colecalciferol	9 (12.7)	5 (6.8)	14 (9.7)
Vitamin d nos	1 (1.4)	8 (10.8)	9 (6.2)
Calcitriol	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIHISTAMINES FOR SYSTEMIC USE	10 (14.1)	13 (17.6)	23 (15.9)
Loratadine	2 (2.8)	4 (5.4)	6 (4.1)
Fexofenadine hydrochloride	3 (4.2)	2 (2.7)	5 (3.4)
Desloratadine	2 (2.8)	1 (1.4)	3 (2.1)
Bilastine	1 (1.4)	1 (1.4)	2 (1.4)
Fexofenadine	0	2 (2.7)	2 (1.4)
Bepotastine besilate	0	1 (1.4)	1 (0.7)
Ebastine	1 (1.4)	0	1 (0.7)
Ketotifen	0	1 (1.4)	1 (0.7)
Olopatadine hydrochloride	0	1 (1.4)	1 (0.7)
Rupatadine	1 (1.4)	0	1 (0.7)
Rupatadine fumarate	0	1 (1.4)	1 (0.7)

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or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER EMOLLIENTS AND PROTECTIVES	18 (25.4)	4 (5.4)	22 (15.2)
Mucopolysaccharide polysulfuric acid ester	3 (4.2)	3 (4.1)	6 (4.1)
Other emollients and protectives	4 (5.6)	0	4 (2.8)
Avena sativa seed;glycerol;paraffin, liquid	2 (2.8)	0	2 (1.4)
Benzalkonium chloride;chlorhexidine hydrochloride;isopropyl myristate;paraffin, liquid	2 (2.8)	0	2 (1.4)
Ceramide;cholesterol;stearic acid;vitellaria paradoxa subsp. paradoxa	1 (1.4)	1 (1.4)	2 (1.4)
Ceramide;palmidrol;vitellaria paradoxa subsp. paradoxa	2 (2.8)	0	2 (1.4)
Glycerol	2 (2.8)	0	2 (1.4)
Glycerol;paraffin, liquid;white soft paraffin	1 (1.4)	0	1 (0.7)
Heparinoid	1 (1.4)	0	1 (0.7)
Paraffin	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
CORTICOSTEROIDS, POTENT (GROUP III)	18 (25.4)	1 (1.4)	19 (13.1)
Betamethasone	5 (7.0)	1 (1.4)	6 (4.1)
Betamethasone butyrate propionate	5 (7.0)	0	5 (3.4)
Betamethasone valerate	3 (4.2)	0	3 (2.1)
Betamethasone dipropionate	2 (2.8)	0	2 (1.4)
Methylprednisolone aceponate	2 (2.8)	0	2 (1.4)
Fludroxycortide	1 (1.4)	0	1 (0.7)
Mometasone	1 (1.4)	0	1 (0.7)
Prednicarbate	1 (1.4)	0	1 (0.7)
Ulobetasol propionate	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
PYRAZOLONES	7 (9.9)	11 (14.9)	18 (12.4)
Metamizole sodium	4 (5.6)	9 (12.2)	13 (9.0)
Metamizole	2 (2.8)	1 (1.4)	3 (2.1)
Caffeine;isometheptene mucate;metamizole sodium	0	1 (1.4)	1 (0.7)
Caffeine;isometheptene;metamizole	0	1 (1.4)	1 (0.7)
Metamizole sodium monohydrate	1 (1.4)	0	1 (0.7)
PROTON PUMP INHIBITORS	7 (9.9)	10 (13.5)	17 (11.7)
Pantoprazole	6 (8.5)	5 (6.8)	11 (7.6)
Omeprazole	1 (1.4)	2 (2.7)	3 (2.1)
Esomeprazole	0	1 (1.4)	1 (0.7)
Pantoprazole sodium sesquihydrate	0	1 (1.4)	1 (0.7)
Rabeprazole	0	1 (1.4)	1 (0.7)
Rabeprazole sodium	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
GLUCOCORTICOIDS	8 (11.3)	6 (8.1)	14 (9.7)
Budesonide	1 (1.4)	2 (2.7)	3 (2.1)
Prednisolone	1 (1.4)	2 (2.7)	3 (2.1)
Betamethasone	2 (2.8)	0	2 (1.4)
Prednisone	2 (2.8)	0	2 (1.4)
Beclometasone dipropionate	0	1 (1.4)	1 (0.7)
Fluticasone propionate	1 (1.4)	0	1 (0.7)
Methylprednisolone	1 (1.4)	0	1 (0.7)
Methylprednisolone sodium succinate	0	1 (1.4)	1 (0.7)
Prednisolone sodium phosphate	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANALGESICS AND ANTIPYRETICS	3 (4.2)	11 (14.9)	14 (9.7)
Duloxetine hydrochloride	0	4 (5.4)	4 (2.8)
Amitriptyline	1 (1.4)	2 (2.7)	3 (2.1)
Cannabis sativa	0	2 (2.7)	2 (1.4)
Duloxetine	0	2 (2.7)	2 (1.4)
Amitriptyline hydrochloride	1 (1.4)	0	1 (0.7)
Cannabidiol	1 (1.4)	0	1 (0.7)
Dronabinol	0	1 (1.4)	1 (0.7)
Isatis tinctoria leaf;isatis tinctoria root	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
BENZODIAZEPINE DERIVATIVES	7 (9.9)	6 (8.1)	13 (9.0)
Clonazepam	3 (4.2)	3 (4.1)	6 (4.1)
Alprazolam	2 (2.8)	0	2 (1.4)
Estazolam	1 (1.4)	1 (1.4)	2 (1.4)
Bromazepam	1 (1.4)	0	1 (0.7)
Diazepam	1 (1.4)	0	1 (0.7)
Etizolam	0	1 (1.4)	1 (0.7)
Lorazepam	1 (1.4)	0	1 (0.7)
Midazolam	0	1 (1.4)	1 (0.7)
OTHER ANTIBIOTICS FOR TOPICAL USE	8 (11.3)	5 (6.8)	13 (9.0)
Mupirocin	5 (7.0)	3 (4.1)	8 (5.5)
Fusidic acid	3 (4.2)	0	3 (2.1)
Bacitracin zinc;neomycin sulfate	0	1 (1.4)	1 (0.7)
Bacitracin;neomycin	0	1 (1.4)	1 (0.7)
Erythromycin	1 (1.4)	0	1 (0.7)

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Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OPIOIDS IN COMBINATION WITH NON-OPIOID ANALGESICS	8 (11.3)	4 (5.4)	12 (8.3)
Codeine phosphate;paracetamol	0	2 (2.7)	2 (1.4)
Dexketoprofen trometamol;tramadol hydrochloride	1 (1.4)	1 (1.4)	2 (1.4)
Paracetamol;tramadol hydrochloride	1 (1.4)	1 (1.4)	2 (1.4)
Caffeine;chlorphenamine maleate;dihydrocodeine phosphate;guaifenesin;methylephedrine hydrochloride-dl;paracetamol;riboflavin	1 (1.4)	0	1 (0.7)
Caffeine;codeine phosphate hemihydrate;paracetamol	1 (1.4)	0	1 (0.7)
Caffeine;codeine phosphate;paracetamol	1 (1.4)	0	1 (0.7)
Codeine;paracetamol	1 (1.4)	0	1 (0.7)
Papaver somniferum;paracetamol	1 (1.4)	0	1 (0.7)
Paracetamol;tramadol	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIEMETICS	5 (7.0)	7 (9.5)	12 (8.3)
Domperidone	1 (1.4)	3 (4.1)	4 (2.8)
Dimenhydrinate	1 (1.4)	2 (2.7)	3 (2.1)
Cyclizine	1 (1.4)	1 (1.4)	2 (1.4)
Metopimazine	2 (2.8)	0	2 (1.4)
Promethazine	0	1 (1.4)	1 (0.7)
OTHER CENTRALLY ACTING AGENTS	5 (7.0)	7 (9.5)	12 (8.3)
Baclofen	1 (1.4)	5 (6.8)	6 (4.1)
Cyclobenzaprine	1 (1.4)	1 (1.4)	2 (1.4)
Tizanidine	2 (2.8)	0	2 (1.4)
Cyclobenzaprine hydrochloride	1 (1.4)	0	1 (0.7)
Diazepam	0	1 (1.4)	1 (0.7)
Eperisone hydrochloride	0	1 (1.4)	1 (0.7)
Tolperisone	1 (1.4)	0	1 (0.7)

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until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,
or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ACETIC ACID DERIVATIVES AND RELATED SUBSTANCES	5 (7.0)	6 (8.1)	11 (7.6)
Diclofenac	1 (1.4)	3 (4.1)	4 (2.8)
Diclofenac sodium	1 (1.4)	2 (2.7)	3 (2.1)
Ketorolac tromethamine	1 (1.4)	1 (1.4)	2 (1.4)
Indometacin	1 (1.4)	0	1 (0.7)
Ketorolac	1 (1.4)	0	1 (0.7)
NATURAL OPIUM ALKALOIDS	3 (4.2)	8 (10.8)	11 (7.6)
Morphine	0	3 (4.1)	3 (2.1)
Naloxone hydrochloride;oxycodone hydrochloride	0	2 (2.7)	2 (1.4)
Oxycodone	0	2 (2.7)	2 (1.4)
Oxycodone hydrochloride	1 (1.4)	1 (1.4)	2 (1.4)
Codeine	1 (1.4)	0	1 (0.7)
Hydromorphone	1 (1.4)	0	1 (0.7)
Morphine sulfate	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OSMOTICALLY ACTING LAXATIVES	6 (8.5)	5 (6.8)	11 (7.6)
Lactulose	0	3 (4.1)	3 (2.1)
Macrogol	2 (2.8)	0	2 (1.4)
Macrogol 3350	1 (1.4)	1 (1.4)	2 (1.4)
Macrogol;potassium;sodium bicarbonate;sodium chloride	1 (1.4)	1 (1.4)	2 (1.4)
Magnesium oxide	1 (1.4)	0	1 (0.7)
Sodium phosphate dibasic (heptahydrate);sodium phosphate monobasic (monohydrate)	1 (1.4)	0	1 (0.7)
PENICILLINS WITH EXTENDED SPECTRUM	6 (8.5)	5 (6.8)	11 (7.6)
Amoxicillin	4 (5.6)	5 (6.8)	9 (6.2)
Amoxicillin trihydrate	2 (2.8)	0	2 (1.4)
ANTIPROPULSIVES	7 (9.9)	3 (4.1)	10 (6.9)
Loperamide hydrochloride	5 (7.0)	1 (1.4)	6 (4.1)
Loperamide	2 (2.8)	2 (2.7)	4 (2.8)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
IMIDAZOLE AND TRIAZOLE DERIVATIVES	7 (9.9)	3 (4.1)	10 (6.9)
Ketoconazole	7 (9.9)	3 (4.1)	10 (6.9)
OTHER ANXIOLYTICS	7 (9.9)	2 (2.7)	9 (6.2)
Escitalopram oxalate	1 (1.4)	1 (1.4)	2 (1.4)
Paroxetine	2 (2.8)	0	2 (1.4)
Venlafaxine hydrochloride	1 (1.4)	1 (1.4)	2 (1.4)
Escitalopram	1 (1.4)	0	1 (0.7)
Pregabalin	1 (1.4)	0	1 (0.7)
Sertraline	1 (1.4)	0	1 (0.7)
OTHER DRUGS FOR PEPTIC ULCER AND GASTRO-OESOPHAGEAL REFLUX DISEASE (GORD)	3 (4.2)	6 (8.1)	9 (6.2)
Rebamipide	2 (2.8)	4 (5.4)	6 (4.1)
Calcium carbonate;sodium alginate;sodium bicarbonate	1 (1.4)	1 (1.4)	2 (1.4)
Teprenone	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
OTHER OPIOIDS	4 (5.6)	5 (6.8)	9 (6.2)
Tramadol	2 (2.8)	4 (5.4)	6 (4.1)
Tapentadol	3 (4.2)	0	3 (2.1)
Tramadol hydrochloride	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	2 (2.8)	7 (9.5)	9 (6.2)
Bupleurum spp.	0	2 (2.7)	2 (1.4)
Unspecified herbal and traditional medicine	1 (1.4)	1 (1.4)	2 (1.4)
Baicalin;buffalo horn;cholic acid;concha margaritifera;gardenia jasminoides fruit;hyodeoxycholic acid;isatis tinctoria root;lonicera japonica flower	0	1 (1.4)	1 (0.7)
Borneol;canarium album ripe fruit;cicada slough;glycyrrhiza spp. root with rhizome;iris domestica rhizome;mentha canadensis herb;platycodon grandiflorus root;prunus mume smoke treated unripe fruit	0	1 (1.4)	1 (0.7)
Chlorella spp.	0	1 (1.4)	1 (0.7)
Crataegus rhipidophylla var. rhipidophylla;passiflora incarnata;valeriana officinalis	0	1 (1.4)	1 (0.7)
Hippophae rhamnoides fruit oil	1 (1.4)	0	1 (0.7)
Valeriana officinalis	0	1 (1.4)	1 (0.7)
Zingiber officinale	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
CORTICOSTEROIDS, WEAK (GROUP I)	8 (11.3)	0	8 (5.5)
Hydrocortisone	6 (8.5)	0	6 (4.1)
Hydrocortisone acetate	1 (1.4)	0	1 (0.7)
Prednisolone valeroacetate	1 (1.4)	0	1 (0.7)
DRUGS FOR URINARY FREQUENCY AND INCONTINENCE	6 (8.5)	2 (2.7)	8 (5.5)
Mirabegron	3 (4.2)	1 (1.4)	4 (2.8)
Solifenacin	2 (2.8)	0	2 (1.4)
Imidafenacin	1 (1.4)	0	1 (0.7)
Oxybutynin	0	1 (1.4)	1 (0.7)
Tolterodine	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
MUCOLYTICS	3 (4.2)	5 (6.8)	8 (5.5)
Acetylcysteine	1 (1.4)	2 (2.7)	3 (2.1)
Ambroxol hydrochloride	0	2 (2.7)	2 (1.4)
Bromhexine hydrochloride	1 (1.4)	0	1 (0.7)
Carbocisteine	0	1 (1.4)	1 (0.7)
Eprazinone hydrochloride	0	1 (1.4)	1 (0.7)
Sodium chloride	1 (1.4)	0	1 (0.7)
PIPERAZINE DERIVATIVES	5 (7.0)	3 (4.1)	8 (5.5)
Cetirizine	2 (2.8)	1 (1.4)	3 (2.1)
Cetirizine hydrochloride	1 (1.4)	2 (2.7)	3 (2.1)
Hydroxyzine hydrochloride	2 (2.8)	0	2 (1.4)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
PROGESTOGENS	5 (7.0)	3 (4.1)	8 (5.5)
Drospirenone	3 (4.2)	1 (1.4)	4 (2.8)
Desogestrel	2 (2.8)	1 (1.4)	3 (2.1)
Etonogestrel	0	1 (1.4)	1 (0.7)
AMIDES	2 (2.8)	5 (6.8)	7 (4.8)
Lidocaine	1 (1.4)	3 (4.1)	4 (2.8)
Lidocaine hydrochloride	1 (1.4)	1 (1.4)	2 (1.4)
Articaine hydrochloride;epinephrine bitartrate	1 (1.4)	0	1 (0.7)
Epinephrine bitartrate;lidocaine hydrochloride	0	1 (1.4)	1 (0.7)
Epinephrine;lidocaine hydrochloride	0	1 (1.4)	1 (0.7)
Ropivacaine hydrochloride	0	1 (1.4)	1 (0.7)
ANTICHOLINERGICS	4 (5.6)	3 (4.1)	7 (4.8)
Tropicamide	3 (4.2)	1 (1.4)	4 (2.8)
Phenylephrine hydrochloride;tropicamide	1 (1.4)	2 (2.7)	3 (2.1)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ASCORBIC ACID (VITAMIN C), PLAIN	2 (2.8)	5 (6.8)	7 (4.8)
Ascorbic acid	2 (2.8)	5 (6.8)	7 (4.8)
BETA BLOCKING AGENTS, SELECTIVE	5 (7.0)	2 (2.7)	7 (4.8)
Bisoprolol	3 (4.2)	1 (1.4)	4 (2.8)
Bisoprolol fumarate	1 (1.4)	0	1 (0.7)
Metoprolol	0	1 (1.4)	1 (0.7)
Nebivolol hydrochloride	1 (1.4)	0	1 (0.7)
CORTICOSTEROIDS, MODERATELY POTENT (GROUP II)	5 (7.0)	2 (2.7)	7 (4.8)
Triamcinolone acetonide	1 (1.4)	2 (2.7)	3 (2.1)
Desonide	2 (2.8)	0	2 (1.4)
Clobetasone butyrate	1 (1.4)	0	1 (0.7)
Dexamethasone propionate	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
THIRD-GENERATION CEPHALOSPORINS	5 (7.0)	2 (2.7)	7 (4.8)
Cefixime	2 (2.8)	0	2 (1.4)
Ceftriaxone	1 (1.4)	1 (1.4)	2 (1.4)
Cefcapene pivoxil hydrochloride	0	1 (1.4)	1 (0.7)
Cefdinir	1 (1.4)	0	1 (0.7)
Cefditoren	1 (1.4)	0	1 (0.7)
Cefditoren pivoxil	1 (1.4)	0	1 (0.7)
Cefoperazone sodium;sulbactam sodium	1 (1.4)	0	1 (0.7)
Cefpodoxime proxetil	1 (1.4)	0	1 (0.7)
AGENTS FOR DERMATITIS, EXCLUDING CORTICOSTEROIDS	5 (7.0)	1 (1.4)	6 (4.1)
Pimecrolimus	5 (7.0)	1 (1.4)	6 (4.1)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
COMBINATIONS OF PENICILLINS, INCL. BETA-LACTAMASE INHIBITORS	1 (1.4)	5 (6.8)	6 (4.1)
Amoxicillin;clavulanic acid	1 (1.4)	3 (4.1)	4 (2.8)
Amoxicillin trihydrate;clavulanate potassium	0	1 (1.4)	1 (0.7)
Amoxicillin;clavulanate potassium	0	1 (1.4)	1 (0.7)
HMG COA REDUCTASE INHIBITORS	4 (5.6)	2 (2.7)	6 (4.1)
Rosuvastatin	1 (1.4)	2 (2.7)	3 (2.1)
Atorvastatin	2 (2.8)	0	2 (1.4)
Rosuvastatin calcium	1 (1.4)	0	1 (0.7)
IRON BIVALENT, ORAL PREPARATIONS	4 (5.6)	2 (2.7)	6 (4.1)
Ferrous sulfate	1 (1.4)	1 (1.4)	2 (1.4)
Iron polysaccharide complex	1 (1.4)	1 (1.4)	2 (1.4)
Ferrous sodium citrate	1 (1.4)	0	1 (0.7)
Iron	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER AGENTS FOR LOCAL ORAL TREATMENT	5 (7.0)	1 (1.4)	6 (4.1)
Calendula officinalis;camellia sinensis;handroanthus impetiginosus;hyaluronic acid;malva spp.;plantago spp.;propolis;sisymbrium officinale	1 (1.4)	0	1 (0.7)
Cineole;menthol;methyl salicylate;thymol	1 (1.4)	0	1 (0.7)
Dipotassium glycyrrhizate;malva sylvestris;xylitol;zinc oxide	1 (1.4)	0	1 (0.7)
Lidocaine hydrochloride;matricaria chamomilla flower	0	1 (1.4)	1 (0.7)
Other agents for local oral treatment	1 (1.4)	0	1 (0.7)
Rheum spp.;salicylic acid	0	1 (1.4)	1 (0.7)
Sodium gualenate hydrate	1 (1.4)	0	1 (0.7)
Triester glycerol oxide	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIDEPRESSANTS	6 (8.5)	0	6 (4.1)
Mirtazapine	4 (5.6)	0	4 (2.8)
Desvenlafaxine	1 (1.4)	0	1 (0.7)
Trazodone	1 (1.4)	0	1 (0.7)
Venlafaxine	1 (1.4)	0	1 (0.7)
SELECTIVE BETA-2-ADRENORECEPTOR AGONISTS	4 (5.6)	2 (2.7)	6 (4.1)
Salbutamol	4 (5.6)	2 (2.7)	6 (4.1)
Procaterol hydrochloride	1 (1.4)	0	1 (0.7)
SEROTONIN (5HT3) ANTAGONISTS	3 (4.2)	3 (4.1)	6 (4.1)
Ondansetron	3 (4.2)	2 (2.7)	5 (3.4)
Dolasetron mesilate	0	1 (1.4)	1 (0.7)
Ondansetron hydrochloride	0	1 (1.4)	1 (0.7)
Palonosetron hydrochloride	0	1 (1.4)	1 (0.7)

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until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,
or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ANTIDIARRHEAL MICROORGANISMS	3 (4.2)	2 (2.7)	5 (3.4)
Bacillus clausii	1 (1.4)	0	1 (0.7)
Bacillus coagulans;bifidobacterium nos;lactobacillus acidophilus;lactobacillus casei;vitamin b nos;zinc	1 (1.4)	0	1 (0.7)
Bifidobacterium lactis	1 (1.4)	0	1 (0.7)
Enterococcus faecalis	0	1 (1.4)	1 (0.7)
Lactobacillus acidophilus;zinc oxide	1 (1.4)	0	1 (0.7)
Lactomin	0	1 (1.4)	1 (0.7)
CORTICOSTEROIDS	3 (4.2)	2 (2.7)	5 (3.4)
Budesonide	0	1 (1.4)	1 (0.7)
Mometasone	1 (1.4)	0	1 (0.7)
Mometasone furoate	0	1 (1.4)	1 (0.7)
Tixocortol pivalate	1 (1.4)	0	1 (0.7)
Triamcinolone acetonide	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
CORTICOSTEROIDS FOR LOCAL ORAL TREATMENT	5 (7.0)	0	5 (3.4)
Dexamethasone	3 (4.2)	0	3 (2.1)
Dexamethasone sodium phosphate	1 (1.4)	0	1 (0.7)
Triamcinolone acetonide	1 (1.4)	0	1 (0.7)
COXIBS	1 (1.4)	4 (5.4)	5 (3.4)
Celecoxib	0	2 (2.7)	2 (1.4)
Etoricoxib	1 (1.4)	1 (1.4)	2 (1.4)
Parecoxib sodium	0	1 (1.4)	1 (0.7)
FIRST-GENERATION CEPHALOSPORINS	3 (4.2)	2 (2.7)	5 (3.4)
Cefalexin	3 (4.2)	2 (2.7)	5 (3.4)
ORIPAVINE DERIVATIVES	2 (2.8)	3 (4.1)	5 (3.4)
Buprenorphine	1 (1.4)	3 (4.1)	4 (2.8)
Buprenorphine;naloxone	1 (1.4)	0	1 (0.7)

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Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIMIGRAINE PREPARATIONS	2 (2.8)	3 (4.1)	5 (3.4)
Venlafaxine	0	2 (2.7)	2 (1.4)
Amitriptyline hydrochloride	1 (1.4)	0	1 (0.7)
Flunarizine	1 (1.4)	0	1 (0.7)
Ginkgo biloba;riboflavin;ubidecarenone	0	1 (1.4)	1 (0.7)
OTHER OPHTHALMOLOGICALS	4 (5.6)	1 (1.4)	5 (3.4)
Acetylcysteine	0	1 (1.4)	1 (0.7)
Carmellose sodium	1 (1.4)	0	1 (0.7)
Chondroitin sulfate sodium;glucose;potassium chloride;sodium chloride	1 (1.4)	0	1 (0.7)
Hyaluronate sodium	1 (1.4)	0	1 (0.7)
Hyaluronate sodium;trehalose	1 (1.4)	0	1 (0.7)
Paraffin, liquid;white soft paraffin	1 (1.4)	0	1 (0.7)
Retinol palmitate	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
PROGESTOGENS AND ESTROGENS, FIXED COMBINATIONS	3 (4.2)	2 (2.7)	5 (3.4)
Ethinylestradiol;levonorgestrel	2 (2.8)	1 (1.4)	3 (2.1)
Desogestrel;ethinylestradiol	1 (1.4)	0	1 (0.7)
Estradiol;nomegestrol acetate	0	1 (1.4)	1 (0.7)
ACE INHIBITORS, PLAIN	4 (5.6)	0	4 (2.8)
Ramipril	2 (2.8)	0	2 (1.4)
Enalapril maleate	1 (1.4)	0	1 (0.7)
Lisinopril	1 (1.4)	0	1 (0.7)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS), PLAIN	2 (2.8)	2 (2.7)	4 (2.8)
Losartan	1 (1.4)	1 (1.4)	2 (1.4)
Candesartan	1 (1.4)	0	1 (0.7)
Valsartan	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ANTIEMETICS AND ANTINAUSEANTS	4 (5.6)	0	4 (2.8)
Metoclopramide	3 (4.2)	0	3 (2.1)
Metoclopramide hydrochloride	1 (1.4)	0	1 (0.7)
ANTIINFLAMMATORY PREPARATIONS, NON-STEROIDS FOR TOPICAL USE	2 (2.8)	2 (2.7)	4 (2.8)
Loxoprofen sodium dihydrate	1 (1.4)	1 (1.4)	2 (1.4)
Diclofenac	1 (1.4)	0	1 (0.7)
Felbinac	1 (1.4)	0	1 (0.7)
Ketoprofen	0	1 (1.4)	1 (0.7)
BULK-FORMING LAXATIVES	2 (2.8)	2 (2.7)	4 (2.8)
Polycarbophil calcium	1 (1.4)	1 (1.4)	2 (1.4)
Chondrus crispus	0	1 (1.4)	1 (0.7)
Plantago ovata	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
CORTICOSTEROIDS AND ANTIINFECTIVES IN COMBINATION	2 (2.8)	2 (2.7)	4 (2.8)
Ciprofloxacin hydrochloride;dexamethasone	1 (1.4)	1 (1.4)	2 (1.4)
Betamethasone;chloramphenicol	1 (1.4)	0	1 (0.7)
Chloramphenicol;dexamethasone;tetracaine hydrochloride	0	1 (1.4)	1 (0.7)
CORTICOSTEROIDS, POTENT, COMBINATIONS WITH ANTIBIOTICS	3 (4.2)	1 (1.4)	4 (2.8)
Betamethasone valerate;gentamicin sulfate	2 (2.8)	0	2 (1.4)
Betamethasone valerate;fusidic acid	1 (1.4)	0	1 (0.7)
Fluocinolone acetonide;neomycin	0	1 (1.4)	1 (0.7)
CORTICOSTEROIDS, VERY POTENT (GROUP IV)	4 (5.6)	0	4 (2.8)
Clobetasol propionate	3 (4.2)	0	3 (2.1)
Clobetasol	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
COVID-19 VACCINES	1 (1.4)	3 (4.1)	4 (2.8)
Tozinameran	1 (1.4)	2 (2.7)	3 (2.1)
Covid-19 vaccine	0	1 (1.4)	1 (0.7)
ETHERS, CHEMICALLY CLOSE TO ANTIHISTAMINES	3 (4.2)	1 (1.4)	4 (2.8)
Caffeine;metamizole sodium;orphenadrine citrate	3 (4.2)	1 (1.4)	4 (2.8)
LIVER THERAPY	2 (2.8)	2 (2.7)	4 (2.8)
Polyene phosphatidylcholine	2 (2.8)	1 (1.4)	3 (2.1)
Magnesium isoglycyrrhizinate	0	1 (1.4)	1 (0.7)
OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	2 (2.8)	2 (2.7)	4 (2.8)
Clostridium butyricum	2 (2.8)	2 (2.7)	4 (2.8)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIALLERGICS	2 (2.8)	2 (2.7)	4 (2.8)
Olopatadine hydrochloride	1 (1.4)	1 (1.4)	2 (1.4)
Epinastine hydrochloride	0	1 (1.4)	1 (0.7)
Ketotifen fumarate	1 (1.4)	0	1 (0.7)
OTHER ANTIINFLAMMATORY AND ANTIRHEUMATIC AGENTS, NON-STEROIDS	2 (2.8)	2 (2.7)	4 (2.8)
Rabbit vaccinia extract	0	2 (2.7)	2 (1.4)
Chondroitin sulfate	1 (1.4)	0	1 (0.7)
Morniflumate	1 (1.4)	0	1 (0.7)
Nimesulide	1 (1.4)	0	1 (0.7)
OTHER DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	4 (5.6)	0	4 (2.8)
Phloroglucinol	2 (2.8)	0	2 (1.4)
Pinaverium bromide	1 (1.4)	0	1 (0.7)
Simeticone	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
PEROXIDES	4 (5.6)	0	4 (2.8)
Benzoyl peroxide	4 (5.6)	0	4 (2.8)
RETINOIDS FOR TOPICAL USE IN ACNE	4 (5.6)	0	4 (2.8)
Adapalene	1 (1.4)	0	1 (0.7)
Clindamycin phosphate;tretinoin	1 (1.4)	0	1 (0.7)
Tazarotene	1 (1.4)	0	1 (0.7)
Tretinoin	1 (1.4)	0	1 (0.7)
SECOND-GENERATION CEPHALOSPORINS	1 (1.4)	3 (4.1)	4 (2.8)
Cefaclor	1 (1.4)	0	1 (0.7)
Cefprozil	0	1 (1.4)	1 (0.7)
Cefuroxime	0	1 (1.4)	1 (0.7)
Cefuroxime sodium	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
SELECTIVE SEROTONIN (5HT1) AGONISTS	2 (2.8)	2 (2.7)	4 (2.8)
Rizatriptan	1 (1.4)	1 (1.4)	2 (1.4)
Sumatriptan	0	2 (2.7)	2 (1.4)
Zolmitriptan	1 (1.4)	0	1 (0.7)
SELECTIVE SEROTONIN REUPTAKE INHIBITORS	3 (4.2)	1 (1.4)	4 (2.8)
Sertraline	2 (2.8)	0	2 (1.4)
Citalopram	0	1 (1.4)	1 (0.7)
Escitalopram	1 (1.4)	0	1 (0.7)
Escitalopram oxalate	1 (1.4)	0	1 (0.7)
SULFONAMIDES, PLAIN	2 (2.8)	2 (2.7)	4 (2.8)
Furosemide	1 (1.4)	1 (1.4)	2 (1.4)
Acetazolamide	0	1 (1.4)	1 (0.7)
Indapamide	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
THYROID HORMONES	1 (1.4)	3 (4.1)	4 (2.8)
Levothyroxine	1 (1.4)	2 (2.7)	3 (2.1)
Levothyroxine sodium	0	1 (1.4)	1 (0.7)
ADRENERGICS IN COMBINATION WITH CORTICOSTEROIDS OR OTHER DRUGS, EXCL. ANTICHOLINERGICS	0	3 (4.1)	3 (2.1)
Budesonide;formoterol fumarate	0	2 (2.7)	2 (1.4)
Beclometasone;formoterol	0	1 (1.4)	1 (0.7)
ANTISEPTICS	1 (1.4)	2 (2.7)	3 (2.1)
Dequalinium chloride	0	1 (1.4)	1 (0.7)
Hexamidine	0	1 (1.4)	1 (0.7)
Hydroxyquinoline	1 (1.4)	0	1 (0.7)
ANTIVIRALS	0	3 (4.1)	3 (2.1)
Aciclovir	0	3 (4.1)	3 (2.1)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
BELLADONNA ALKALOIDS, SEMISYNTHETIC, QUATERNARY AMMONIUM COMPOUNDS	1 (1.4)	2 (2.7)	3 (2.1)
Hyoscine butylbromide	1 (1.4)	2 (2.7)	3 (2.1)
BENZODIAZEPINE RELATED DRUGS	2 (2.8)	1 (1.4)	3 (2.1)
Zolpidem tartrate	2 (2.8)	1 (1.4)	3 (2.1)
BIOFLAVONOIDS	2 (2.8)	1 (1.4)	3 (2.1)
Diosmin	2 (2.8)	1 (1.4)	3 (2.1)
CENTRALLY ACTING SYMPATHOMIMETICS	2 (2.8)	1 (1.4)	3 (2.1)
Lisdexamfetamine mesilate	1 (1.4)	0	1 (0.7)
Methylphenidate	0	1 (1.4)	1 (0.7)
Phenethylamine	1 (1.4)	0	1 (0.7)
COMBINATIONS OF SULFONAMIDES AND TRIMETHOPRIM, INCL. DERIVATIVES	2 (2.8)	1 (1.4)	3 (2.1)
Sulfamethoxazole;trimethoprim	2 (2.8)	1 (1.4)	3 (2.1)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ELECTROLYTE SOLUTIONS	1 (1.4)	2 (2.7)	3 (2.1)
Sodium chloride	1 (1.4)	2 (2.7)	3 (2.1)
Potassium chloride	0	1 (1.4)	1 (0.7)
ENEMAS	2 (2.8)	1 (1.4)	3 (2.1)
Glycerol	0	1 (1.4)	1 (0.7)
Sodium lauryl sulfoacetate	1 (1.4)	0	1 (0.7)
Sodium phosphate dibasic;sodium phosphate monobasic	1 (1.4)	0	1 (0.7)
EXPECTORANTS	2 (2.8)	1 (1.4)	3 (2.1)
Guaifenesin	2 (2.8)	1 (1.4)	3 (2.1)
FAT/CARBOHYDRATES/PROTEINS/MINERALS/VITAMINS, COMBINATIONS	1 (1.4)	2 (2.7)	3 (2.1)
Carbohydrates nos;fats nos;minerals nos;proteins nos;vitamins nos	1 (1.4)	1 (1.4)	2 (1.4)
Casein;herbal oil nos;maltodextrin;minerals nos;trace elements nos;vitamins nos	0	1 (1.4)	1 (0.7)

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treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
FLUOROQUINOLONES	2 (2.8)	1 (1.4)	3 (2.1)
Levofloxacin	1 (1.4)	1 (1.4)	2 (1.4)
Levofloxacin hydrochloride	0	1 (1.4)	1 (0.7)
Norfloxacin	1 (1.4)	0	1 (0.7)
H2-RECEPTOR ANTAGONISTS	1 (1.4)	2 (2.7)	3 (2.1)
Famotidine	1 (1.4)	2 (2.7)	3 (2.1)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
HERBAL DIAPHORETICS AND OTHER HERBAL COUGH AND COLD REMEDIES	1 (1.4)	2 (2.7)	3 (2.1)
Angelica dahurica root;bupleurum spp. root;corydalis bungeana herb;mentha canadensis herb;nepeta tenuifolia spike;perilla frutescens leaf;phragmites australis subsp. australis rhizome; platycodon grandiflorus root;prunus spp. seed;pueraria montana var. lobata root;saposhnikovia divaricata root	0	1 (1.4)	1 (0.7)
Arctium lappa fruit;forsythia suspensa fruit;glycine max fermented seed;glycyrrhiza spp. root with rhizome;lonicera japonica flower bud;lophatherum gracile leaf with stem;mentha canadensis herb; nepetatenuifolia herb;platycodon grandiflorus root	1 (1.4)	0	1 (0.7)
Bupleurum chinense root;forsythia suspensa fruit;glycyrrhiza uralensis root;isatis tinctoria root;patrinia scabiosifolia;phragmites australis subsp. australis rhizome;reynoutria japonica root; verbena officinalis	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
IMIDAZOLE DERIVATIVES	2 (2.8)	1 (1.4)	3 (2.1)
Clotrimazole	1 (1.4)	0	1 (0.7)
Cow bezoar;metronidazole	0	1 (1.4)	1 (0.7)
Metronidazole	1 (1.4)	0	1 (0.7)
LINCOSAMIDES	2 (2.8)	1 (1.4)	3 (2.1)
Clindamycin	2 (2.8)	0	2 (1.4)
Clindamycin phosphate	0	1 (1.4)	1 (0.7)
MAGNESIUM	2 (2.8)	1 (1.4)	3 (2.1)
Magnesium	1 (1.4)	0	1 (0.7)
Magnesium citrate	0	1 (1.4)	1 (0.7)
Magnesium glycinate	1 (1.4)	0	1 (0.7)
Magnesium oxide	0	1 (1.4)	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
MELATONIN RECEPTOR AGONISTS	2 (2.8)	1 (1.4)	3 (2.1)
Melatonin	2 (2.8)	1 (1.4)	3 (2.1)
NITROFURAN DERIVATIVES	2 (2.8)	1 (1.4)	3 (2.1)
Nitrofurantoin	2 (2.8)	1 (1.4)	3 (2.1)
OPIUM ALKALOIDS AND DERIVATIVES	2 (2.8)	1 (1.4)	3 (2.1)
Chlorphenamine maleate;dihydrocodeine phosphate;methylephedrine hydrochloride-dl	0	1 (1.4)	1 (0.7)
Codeine	1 (1.4)	0	1 (0.7)
Dextromethorphan hydrobromide	1 (1.4)	0	1 (0.7)
OTHER ANTI-ACNE PREPARATIONS FOR TOPICAL USE	3 (4.2)	0	3 (2.1)
Chlorhexidine	2 (2.8)	0	2 (1.4)
Lauric acid;salicylic acid;zinc acetate	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIFUNGALS FOR TOPICAL USE	3 (4.2)	0	3 (2.1)
Amorolfine hydrochloride	1 (1.4)	0	1 (0.7)
Ciclopirox olamine;hydroxypropyl chitosan	1 (1.4)	0	1 (0.7)
Selenium sulfide	1 (1.4)	0	1 (0.7)
OTHER ANTIPRURITICS	2 (2.8)	1 (1.4)	3 (2.1)
Calamine	1 (1.4)	0	1 (0.7)
Doxepin	0	1 (1.4)	1 (0.7)
Urea-cresol-sulfonate sodium	1 (1.4)	0	1 (0.7)
OTHER DERMATOLOGICALS	3 (4.2)	0	3 (2.1)
Ivermectin	2 (2.8)	0	2 (1.4)
Other dermatologicals	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
OTHER NERVOUS SYSTEM DRUGS	1 (1.4)	2 (2.7)	3 (2.1)
Mecobalamin	0	2 (2.7)	2 (1.4)
Gabapentin	1 (1.4)	0	1 (0.7)
PHENYLPIPERIDINE DERIVATIVES	0	3 (4.1)	3 (2.1)
Fentanyl	0	2 (2.7)	2 (1.4)
Fentanyl citrate	0	1 (1.4)	1 (0.7)
Pethidine hydrochloride	0	1 (1.4)	1 (0.7)
PLATELET AGGREGATION INHIBITORS EXCL. HEPARIN	1 (1.4)	2 (2.7)	3 (2.1)
Acetylsalicylic acid	1 (1.4)	2 (2.7)	3 (2.1)
POTASSIUM	2 (2.8)	1 (1.4)	3 (2.1)
Potassium chloride	2 (2.8)	1 (1.4)	3 (2.1)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
PROPULSIVES	2 (2.8)	1 (1.4)	3 (2.1)
Cinitapride tartrate	1 (1.4)	0	1 (0.7)
Domperidone	0	1 (1.4)	1 (0.7)
Metoclopramide	1 (1.4)	0	1 (0.7)
SALICYLIC ACID AND DERIVATIVES	1 (1.4)	2 (2.7)	3 (2.1)
Acetylsalicylic acid	1 (1.4)	2 (2.7)	3 (2.1)
Acetylsalicylic acid;ascorbic acid	1 (1.4)	0	1 (0.7)
SOFT PARAFFIN AND FAT PRODUCTS	3 (4.2)	0	3 (2.1)
Light liquid paraffin;white soft paraffin	2 (2.8)	0	2 (1.4)
Petrolatum	1 (1.4)	0	1 (0.7)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	1 (1.4)	2 (2.7)	3 (2.1)
Calcium chloride;potassium chloride;sodium chloride;sodium lactate	1 (1.4)	1 (1.4)	2 (1.4)
Glucose;sodium chloride	0	2 (2.7)	2 (1.4)

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Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
VITAMIN B-COMPLEX, PLAIN	1 (1.4)	2 (2.7)	3 (2.1)
Vitamin b complex	1 (1.4)	2 (2.7)	3 (2.1)
3-OXOANDROSTEN (4) DERIVATIVES	0	2 (2.7)	2 (1.4)
Testosterone	0	2 (2.7)	2 (1.4)
Testosterone cipionate	0	1 (1.4)	1 (0.7)
ALPHA-ADRENORECEPTOR ANTAGONISTS	1 (1.4)	1 (1.4)	2 (1.4)
Prazosin	1 (1.4)	0	1 (0.7)
Tamsulosin	0	1 (1.4)	1 (0.7)
AMINOALKYL ETHERS	1 (1.4)	1 (1.4)	2 (1.4)
Clemastine fumarate	1 (1.4)	0	1 (0.7)
Diphenhydramine hydrochloride	0	1 (1.4)	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ANTIBIOTICS	2 (2.8)	0	2 (1.4)
Tobramycin	1 (1.4)	0	1 (0.7)
Tyrothricin	1 (1.4)	0	1 (0.7)
ANTIINFECTIVES AND ANTISEPTICS FOR LOCAL ORAL TREATMENT	2 (2.8)	0	2 (1.4)
Boric acid	1 (1.4)	0	1 (0.7)
Metronidazole	1 (1.4)	0	1 (0.7)
BETA BLOCKING AGENTS	0	2 (2.7)	2 (1.4)
Brimonidine tartrate;timolol maleate	0	1 (1.4)	1 (0.7)
Latanoprost;timolol maleate	0	1 (1.4)	1 (0.7)
BETA-LACTAMASE INHIBITORS	1 (1.4)	1 (1.4)	2 (1.4)
Clavulanic acid	1 (1.4)	1 (1.4)	2 (1.4)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
BILE ACIDS AND DERIVATIVES	2 (2.8)	0	2 (1.4)
Ursodeoxycholic acid	2 (2.8)	0	2 (1.4)
CAPSAICIN AND SIMILAR AGENTS	1 (1.4)	1 (1.4)	2 (1.4)
Capsaicin	1 (1.4)	1 (1.4)	2 (1.4)
CARBAMIC ACID ESTERS	0	2 (2.7)	2 (1.4)
Caffeine;carisoprodol;diclofenac sodium;paracetamol	0	1 (1.4)	1 (0.7)
Methocarbamol	0	1 (1.4)	1 (0.7)
COMBINATIONS OF VITAMINS	2 (2.8)	0	2 (1.4)
Ascorbic acid;vitamin d nos	1 (1.4)	0	1 (0.7)
Colecalciferol;menaquinone-7	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
DIAZEPINES, OXAZEPINES, THIAZEPINES AND OXEPINES	2 (2.8)	0	2 (1.4)
Olanzapine	1 (1.4)	0	1 (0.7)
Quetiapine	1 (1.4)	0	1 (0.7)
Quetiapine fumarate	1 (1.4)	0	1 (0.7)
DIHYDROPYRIDINE DERIVATIVES	1 (1.4)	1 (1.4)	2 (1.4)
Amlodipine	1 (1.4)	0	1 (0.7)
Nifedipine	0	1 (1.4)	1 (0.7)
DIPHENYLPROPYLAMINE DERIVATIVES	1 (1.4)	1 (1.4)	2 (1.4)
Methadone	1 (1.4)	1 (1.4)	2 (1.4)
DIRECT FACTOR XA INHIBITORS	0	2 (2.7)	2 (1.4)
Rivaroxaban	0	2 (2.7)	2 (1.4)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
FIBRATES	1 (1.4)	1 (1.4)	2 (1.4)
Fenofibrate	1 (1.4)	1 (1.4)	2 (1.4)
GLYCOPEPTIDE ANTIBACTERIALS	1 (1.4)	1 (1.4)	2 (1.4)
Vancomycin	1 (1.4)	0	1 (0.7)
Vancomycin hydrochloride	0	1 (1.4)	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
HERBAL COUGH AND COLD REMEDIES, OTHER	1 (1.4)	1 (1.4)	2 (1.4)
Anemarrhena asphodeloides rhizome;calcium sulfate dihydrate;isatis tinctoria leaf;prunus spp. seed;rehmannia glutinosa root tuber;scrophularia ningpoensis root;trollius chinensis flower	1 (1.4)	0	1 (0.7)
Angelica dahurica root;areca catechu fruit peel;atractylodes macrocephala rhizome;citrus x aurantium fruit peel;glycyrrhiza spp. root with rhizome;magnolia officinalis bark;perilla frutescens leaf; pinellia ternata tuber;platycodon grandiflorus root;pogostemon cablin herb;poria cocos sclerotium;zingiber officinale rhizome;ziziphus jujuba fruit	0	1 (1.4)	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
HERBAL EXPECTORANTS AND EMOLLIENTS	1 (1.4)	1 (1.4)	2 (1.4)
Adenophora spp. root;citrus maxima peel;fritillaria cirrhosa bulb;glycyrrhiza uralensis root;honey;menthol;pinellia ternata rhizome;platycodon grandiflorus root;polygala spp. root; poria cocos sclerotium;prunus armeniaca seed;rhaphiolepis bibas leaf;schisandra chinensis fruit;trichosanthes spp. seed;tussilago farfara flower bud;zingiber officinale fresh rhizome	0	1 (1.4)	1 (0.7)
Aster tataricus root with rhizome;citrus x aurantium epicarp;fritillaria spp. bulb;mentha canadensis herb;pinellia ternata rhizome;platycodon grandiflorus root;polygala spp. root;prunus spp. seed; rhaphiolepis bibas leaf;tussilago farfara flower bud	1 (1.4)	0	1 (0.7)
INSULINS AND ANALOGUES FOR INJECTION, FAST-ACTING	1 (1.4)	1 (1.4)	2 (1.4)
Insulin	0	1 (1.4)	1 (0.7)
Insulin glulisine	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
INTRAUTERINE CONTRACEPTIVES	1 (1.4)	1 (1.4)	2 (1.4)
Levonorgestrel	1 (1.4)	1 (1.4)	2 (1.4)
LOCAL ANESTHETICS	1 (1.4)	1 (1.4)	2 (1.4)
Oxybuprocaine	1 (1.4)	1 (1.4)	2 (1.4)
MACROLIDES	1 (1.4)	1 (1.4)	2 (1.4)
Azithromycin	0	1 (1.4)	1 (0.7)
Roxithromycin	1 (1.4)	0	1 (0.7)
NATURAL AND SEMISYNTHETIC ESTROGENS, PLAIN	0	2 (2.7)	2 (1.4)
Ethinylestradiol	0	2 (2.7)	2 (1.4)
NUCLEOSIDES AND NUCLEOTIDES EXCL. REVERSE TRANSCRIPTASE INHIBITORS	2 (2.8)	0	2 (1.4)
Famciclovir	1 (1.4)	0	1 (0.7)
Valaciclovir	1 (1.4)	0	1 (0.7)

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Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER ANTIBACTERIALS	2 (2.8)	0	2 (1.4)
Fosfomycin trometamol	2 (2.8)	0	2 (1.4)
OTHER ANTIEPILEPTICS	0	2 (2.7)	2 (1.4)
Lamotrigine	0	1 (1.4)	1 (0.7)
Levetiracetam	0	1 (1.4)	1 (0.7)
OTHER ANTIPSYCHOTICS	1 (1.4)	1 (1.4)	2 (1.4)
Risperidone	0	1 (1.4)	1 (0.7)
Valproate semisodium	1 (1.4)	0	1 (0.7)
OTHER CARDIAC PREPARATIONS	1 (1.4)	1 (1.4)	2 (1.4)
Ivabradine	0	1 (1.4)	1 (0.7)
Ubidecarenone	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER CHEMOTHERAPEUTICS	2 (2.8)	0	2 (1.4)
Metronidazole	2 (2.8)	0	2 (1.4)
OTHER DRUGS FOR CONSTIPATION	1 (1.4)	1 (1.4)	2 (1.4)
Cannabis sativa fruit;citrus x aurantium unripe fruit;magnolia officinalis bark;prunus spp. seed;rheum spp. root with stem	0	1 (1.4)	1 (0.7)
Prucalopride	1 (1.4)	0	1 (0.7)
OTHER GENERAL ANESTHETICS	1 (1.4)	1 (1.4)	2 (1.4)
Ketamine	1 (1.4)	0	1 (0.7)
Propofol	0	1 (1.4)	1 (0.7)
OTHER IMMUNOSTIMULANTS	1 (1.4)	1 (1.4)	2 (1.4)
Ascorbic acid;saccharomyces cerevisiae;zinc oxide	0	1 (1.4)	1 (0.7)
Glutathione	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER INTESTINAL ADSORBENTS	2 (2.8)	0	2 (1.4)
Montmorillonite	2 (2.8)	0	2 (1.4)
OTHER MINERAL PRODUCTS	1 (1.4)	1 (1.4)	2 (1.4)
Boron	0	1 (1.4)	1 (0.7)
Other mineral products	1 (1.4)	0	1 (0.7)
OTHER MINERAL SUPPLEMENTS	0	2 (2.7)	2 (1.4)
Magnesium carbonate;magnesium chloride;zinc oxide	0	1 (1.4)	1 (0.7)
Magnesium;zinc	0	1 (1.4)	1 (0.7)
OTHER THROAT PREPARATIONS	0	2 (2.7)	2 (1.4)
Tranexamic acid	0	2 (2.7)	2 (1.4)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
PHENOTHIAZINES WITH ALIPHATIC SIDE-CHAIN	2 (2.8)	0	2 (1.4)
Chlorpromazine	1 (1.4)	0	1 (0.7)
Levomepromazine	1 (1.4)	0	1 (0.7)
PROGESTOGENS AND ESTROGENS, SEQUENTIAL PREPARATIONS	0	2 (2.7)	2 (1.4)
Dienogest;estradiol valerate	0	1 (1.4)	1 (0.7)
Ethinylestradiol;gestodene	0	1 (1.4)	1 (0.7)
PROSTAGLANDIN ANALOGUES	1 (1.4)	1 (1.4)	2 (1.4)
Latanoprost	0	1 (1.4)	1 (0.7)
Tafluprost	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
SOLUTIONS FOR PARENTERAL NUTRITION	0	2 (2.7)	2 (1.4)
Alanine;arginine;aspartic acid;calcium chloride;glucose;glutamic acid;glycine;glycine max seed oil;histidine;isoleucine;leucine;lysine hydrochloride;magnesium sulfate;methionine;phenylalanine; potassium chloride;proline;serine;sodium acetate;sodium glycerophosphate;threonine;tryptophan;tyrosine;valine	0	2 (2.7)	2 (1.4)
SUBSTITUTED ALKYLAMINES	1 (1.4)	1 (1.4)	2 (1.4)
Caffeine;chlorphenamine maleate;hyoscine hydrobromide	0	1 (1.4)	1 (0.7)
Dexchlorpheniramine maleate	1 (1.4)	0	1 (0.7)
SYMPATHOMIMETICS, PLAIN	1 (1.4)	1 (1.4)	2 (1.4)
Oxymetazoline hydrochloride	1 (1.4)	0	1 (0.7)
Tramazoline	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
SYNTHETIC ANTICHOLINERGICS, QUATERNARY AMMONIUM COMPOUNDS	2 (2.8)	0	2 (1.4)
Otilonium bromide	2 (2.8)	0	2 (1.4)
THIAZIDES, PLAIN	1 (1.4)	1 (1.4)	2 (1.4)
Hydrochlorothiazide	1 (1.4)	1 (1.4)	2 (1.4)
VITAMIN B12 (CYANOCOBALAMIN AND ANALOGUES)	0	2 (2.7)	2 (1.4)
Mecobalamin	0	1 (1.4)	1 (0.7)
Vitamin b12 nos	0	1 (1.4)	1 (0.7)
ZINC	2 (2.8)	0	2 (1.4)
Zinc	2 (2.8)	0	2 (1.4)
ACE INHIBITORS AND CALCIUM CHANNEL BLOCKERS	0	1 (1.4)	1 (0.7)
Enalapril maleate;lercanidipine hydrochloride	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ADRENERGIC AND DOPAMINERGIC AGENTS	0	1 (1.4)	1 (0.7)
Ephedrine hydrochloride	0	1 (1.4)	1 (0.7)
Norepinephrine bitartrate	0	1 (1.4)	1 (0.7)
ADRENERGICS IN COMBINATION WITH ANTICHOLINERGICS INCL. TRIPLE COMBINATIONS WITH CORTICOSTEROIDS	0	1 (1.4)	1 (0.7)
Glycopyrronium bromide;indacaterol acetate;mometasone furoate	0	1 (1.4)	1 (0.7)
AMINO ACIDS	0	1 (1.4)	1 (0.7)
Tranexamic acid	0	1 (1.4)	1 (0.7)
AMINO ACIDS AND DERIVATIVES	1 (1.4)	0	1 (0.7)
Ademetionine	1 (1.4)	0	1 (0.7)
ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS) AND CALCIUM CHANNEL BLOCKERS	1 (1.4)	0	1 (0.7)
Amlodipine besilate;irbesartan	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ANTACIDS WITH SODIUM BICARBONATE	1 (1.4)	0	1 (0.7)
Sodium alginate;sodium bicarbonate	1 (1.4)	0	1 (0.7)
ANTIALLERGIC AGENTS, EXCL. CORTICOSTEROIDS	1 (1.4)	0	1 (0.7)
Chlorphenamine maleate;cromoglicate sodium;naphazoline hydrochloride	1 (1.4)	0	1 (0.7)
ANTICHOLINESTERASES	0	1 (1.4)	1 (0.7)
Neostigmine metilsulfate	0	1 (1.4)	1 (0.7)
ANTIHEMORRHAGICS	0	1 (1.4)	1 (0.7)
Aconitum kusnezoffii root;herbal nos	0	1 (1.4)	1 (0.7)
ANTIINFECTIVES	1 (1.4)	0	1 (0.7)
Gramicidin;polymyxin b sulfate	1 (1.4)	0	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ASCORBIC ACID (VITAMIN C), COMBINATIONS	0	1 (1.4)	1 (0.7)
Ascorbic acid;echinacea spp.	0	1 (1.4)	1 (0.7)
AZASPIRODECANEDIONE DERIVATIVES	0	1 (1.4)	1 (0.7)
Buspirone	0	1 (1.4)	1 (0.7)
BETA-LACTAMASE RESISTANT PENICILLINS	1 (1.4)	0	1 (0.7)
Oxacillin	1 (1.4)	0	1 (0.7)
BISPHOSPHONATES	0	1 (1.4)	1 (0.7)
Alendronate sodium	0	1 (1.4)	1 (0.7)
BLOOD SUBSTITUTES AND PLASMA PROTEIN FRACTIONS	0	1 (1.4)	1 (0.7)
Albumin human	0	1 (1.4)	1 (0.7)

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
CALCITONIN GENE-RELATED PEPTIDE (CGRP) ANTAGONISTS	0	1 (1.4)	1 (0.7)
Erenumab	0	1 (1.4)	1 (0.7)
CALCIUM	0	1 (1.4)	1 (0.7)
Calcium	0	1 (1.4)	1 (0.7)
CARBAMIDE PRODUCTS	1 (1.4)	0	1 (0.7)
Urea	1 (1.4)	0	1 (0.7)
CARBAPENEMS	1 (1.4)	0	1 (0.7)
Meropenem	1 (1.4)	0	1 (0.7)
COMBINATIONS AND COMPLEXES OF ALUMINIUM, CALCIUM AND MAGNESIUM COMPOUNDS	1 (1.4)	0	1 (0.7)
Magaldrate	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
COMBINATIONS OF ORAL BLOOD GLUCOSE LOWERING DRUGS	0	1 (1.4)	1 (0.7)
Empagliflozin;metformin hydrochloride	0	1 (1.4)	1 (0.7)
CONTACT LAXATIVES	0	1 (1.4)	1 (0.7)
Bisacodyl	0	1 (1.4)	1 (0.7)
Senna spp.	0	1 (1.4)	1 (0.7)
CORTICOSTEROIDS, PLAIN	1 (1.4)	0	1 (0.7)
Hyaluronate sodium;hydrocortisone sodium phosphate	1 (1.4)	0	1 (0.7)
CORTICOSTEROIDS, WEAK, COMBINATIONS WITH ANTIBIOTICS	0	1 (1.4)	1 (0.7)
Methylprednisolone;neomycin sulfate	0	1 (1.4)	1 (0.7)
DRUGS USED IN ERECTILE DYSFUNCTION	1 (1.4)	0	1 (0.7)
Sildenafil	1 (1.4)	0	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
ENZYME PREPARATIONS	1 (1.4)	0	1 (0.7)
Bile salts;hemicellulase;pancreatin	1 (1.4)	0	1 (0.7)
Pancreatin	1 (1.4)	0	1 (0.7)
ENZYMES	0	1 (1.4)	1 (0.7)
Bromelains	0	1 (1.4)	1 (0.7)
FATTY ACID DERIVATIVES	1 (1.4)	0	1 (0.7)
Valproate sodium	1 (1.4)	0	1 (0.7)
FENAMATES	1 (1.4)	0	1 (0.7)
Mefenamic acid	1 (1.4)	0	1 (0.7)
HALOGENATED HYDROCARBONS	0	1 (1.4)	1 (0.7)
Sevoflurane	0	1 (1.4)	1 (0.7)

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
HEPARIN GROUP	1 (1.4)	0	1 (0.7)
Enoxaparin	1 (1.4)	0	1 (0.7)
HEPARINS OR HEPARINOIDS FOR TOPICAL USE	1 (1.4)	0	1 (0.7)
Heparin	1 (1.4)	0	1 (0.7)
HERBAL ANTIINFLAMMATORY AND ANTIRHEUMATIC REMEDIES	0	1 (1.4)	1 (0.7)
Corydalis bungeana herb;isatis tinctoria root;scutellaria baicalensis root;taraxacum mongolicum herb	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
HERBAL ANTIVIRALS FOR SYSTEMIC USE	0	1 (1.4)	1 (0.7)
Calcium sulfate dihydrate;dryopteris crassirhizoma rhizome;ephedra spp. herb;forsythia suspensa;glycyrrhiza spp. root with rhizome;houttuynia cordata herb;isatis tinctoria root; lonicera japonica flower;menthol;pogostemon cablin herb;prunus spp. seed;rheum spp. root with rhizome;rhodiola crenulata root with rhizome	0	1 (1.4)	1 (0.7)
HERBAL CARMINATIVES	0	1 (1.4)	1 (0.7)
Angelica archangelica root;carum carvi fruit;chelidonium majus herb;glycyrrhiza glabra root;iberis amara;matricaria chamomilla flower;melissa officinalis leaf;mentha x piperita leaf; silybum marianum fruit	0	1 (1.4)	1 (0.7)
HERBAL EMOLLIENTS AND PROTECTIVES CONTAINING MUCILAGE	0	1 (1.4)	1 (0.7)
Aloe vera	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
HERBAL HEALING OF FRACTURED BONES	0	1 (1.4)	1 (0.7)
Angelica sinensis root;dioscorea oppositifolia rhizome;dipsacus asper root;drynaria roosii rhizome;epimedium spp. leaf;eucommia ulmoides stem bark;gynochthodes officinalis root; rehmannia glutinosa processed root tuber;reynoutria multiflora root tuber;tortoise carapace and plastron	0	1 (1.4)	1 (0.7)
HERBAL PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS, OTHER	1 (1.4)	0	1 (0.7)
Arnica montana	1 (1.4)	0	1 (0.7)
HERBAL THROAT PREPARATIONS (TONSILLITIS)	1 (1.4)	0	1 (0.7)
Citrullus lanatus fruit;mirabilite	1 (1.4)	0	1 (0.7)
HERBAL URINARY ANTISEPTICS AND ANTIINFECTIVES	1 (1.4)	0	1 (0.7)
Ascorbic acid;vaccinium macrocarpon	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
INFLUENZA VACCINES	0	1 (1.4)	1 (0.7)
Influenza vaccine	0	1 (1.4)	1 (0.7)
INSULINS AND ANALOGUES FOR INJECTION, LONG-ACTING	1 (1.4)	0	1 (0.7)
Insulin detemir	1 (1.4)	0	1 (0.7)
IRON TRIVALENT, ORAL PREPARATIONS	0	1 (1.4)	1 (0.7)
Ferric hydroxide polymaltose complex	0	1 (1.4)	1 (0.7)
IRON, PARENTERAL PREPARATIONS	1 (1.4)	0	1 (0.7)
Ferric carboxymaltose	1 (1.4)	0	1 (0.7)
LEUKOTRIENE RECEPTOR ANTAGONISTS	0	1 (1.4)	1 (0.7)
Pranlukast	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
MEDICAL GASES	0	1 (1.4)	1 (0.7)
Oxygen	0	1 (1.4)	1 (0.7)
MULTIVITAMINS, PLAIN	0	1 (1.4)	1 (0.7)
Vitamins nos	0	1 (1.4)	1 (0.7)
NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS	0	1 (1.4)	1 (0.7)
Entecavir	0	1 (1.4)	1 (0.7)
OPIOID ANESTHETICS	0	1 (1.4)	1 (0.7)
Remifentanil hydrochloride	0	1 (1.4)	1 (0.7)
Sufentanil citrate	0	1 (1.4)	1 (0.7)
OPIUM DERIVATIVES AND EXPECTORANTS	0	1 (1.4)	1 (0.7)
Camphor;glycyrrhiza spp. root with rhizome;illicium verum oil;papaver somniferum latex;sodium benzoate	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in

treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER AGENTS FOR TREATMENT OF HEMORRHOIDS AND ANAL FISSURES FOR TOPICAL USE	1 (1.4)	0	1 (0.7)
Hyaluronate sodium	1 (1.4)	0	1 (0.7)
OTHER ANTINEOPLASTIC AGENTS	1 (1.4)	0	1 (0.7)
Celecoxib	1 (1.4)	0	1 (0.7)
OTHER ANTIPSORIATICS FOR TOPICAL USE	1 (1.4)	0	1 (0.7)
Calcipotriol	1 (1.4)	0	1 (0.7)
OTHER ANTISEPTICS AND DISINFECTANTS	0	1 (1.4)	1 (0.7)
Benzyl alcohol	0	1 (1.4)	1 (0.7)
OTHER ANTIVIRALS	0	1 (1.4)	1 (0.7)
Umifenovir hydrochloride	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER BLOOD PRODUCTS	0	1 (1.4)	1 (0.7)
Red blood cells	0	1 (1.4)	1 (0.7)
OTHER CARDIAC STIMULANTS	0	1 (1.4)	1 (0.7)
Atropine sulfate	0	1 (1.4)	1 (0.7)
OTHER CICATRIZANTS	1 (1.4)	0	1 (0.7)
Tranilast	1 (1.4)	0	1 (0.7)
OTHER COLD PREPARATIONS	0	1 (1.4)	1 (0.7)
Other cold preparations	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER COUGH SUPPRESSANTS AND EXPECTORANTS	0	1 (1.4)	1 (0.7)
Fritillaria thunbergii bulb;glycyrrhiza spp.;platycodon grandiflorus root;polygala spp. root;poria cocos sclerotium;prunus serotina bark;rhaphiolepis bibas leaf;schisandra spp. fruit; trichosanthes spp. seed;ulmus rubra bark	0	1 (1.4)	1 (0.7)
OTHER DRUGS FOR ACID RELATED DISORDERS	1 (1.4)	0	1 (0.7)
Potassium citrate;sodium citrate	1 (1.4)	0	1 (0.7)
OTHER HYPNOTICS AND SEDATIVES	0	1 (1.4)	1 (0.7)
Doxylamine succinate	0	1 (1.4)	1 (0.7)
OTHER PLAIN VITAMIN PREPARATIONS	1 (1.4)	0	1 (0.7)
Pyridoxine hydrochloride	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER QUATERNARY AMMONIUM COMPOUNDS	0	1 (1.4)	1 (0.7)
Cisatracurium	0	1 (1.4)	1 (0.7)
OTHER SYSTEMIC HEMOSTATICS	0	1 (1.4)	1 (0.7)
Haemocoagulase	0	1 (1.4)	1 (0.7)
OXICAMS	1 (1.4)	0	1 (0.7)
Piroxicam	1 (1.4)	0	1 (0.7)
PAPAVERINE AND DERIVATIVES	0	1 (1.4)	1 (0.7)
Drotaverine hydrochloride	0	1 (1.4)	1 (0.7)
PARAMAGNETIC CONTRAST MEDIA	0	1 (1.4)	1 (0.7)
Gadopentetic acid	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
PARASYMPATHOMIMETICS	0	1 (1.4)	1 (0.7)
Calcium chloride dihydrate;neostigmine metilsulfate;potassium aspartate;sodium bicarbonate;sodium chloride	0	1 (1.4)	1 (0.7)
PERTUSSIS VACCINES	1 (1.4)	0	1 (0.7)
Diphtheria vaccine toxoid;pertussis vaccine acellular 5-component;tetanus vaccine toxoid	1 (1.4)	0	1 (0.7)
PHENOTHIAZINE DERIVATIVES	0	1 (1.4)	1 (0.7)
Mequitazine	0	1 (1.4)	1 (0.7)
PREGNADIEN DERIVATIVES	0	1 (1.4)	1 (0.7)
Gestodene	0	1 (1.4)	1 (0.7)
PREPARATIONS WITH NO EFFECT ON URIC ACID METABOLISM	0	1 (1.4)	1 (0.7)
Colchicine	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
PREPARATIONS WITH SALICYLIC ACID DERIVATIVES	0	1 (1.4)	1 (0.7)
Camphor;capsicum spp. extract;methyl salicylate	0	1 (1.4)	1 (0.7)
PROTEASE INHIBITORS	0	1 (1.4)	1 (0.7)
Nirmatrelvir;ritonavir	0	1 (1.4)	1 (0.7)
RESPIRATORY SYSTEM	1 (1.4)	0	1 (0.7)
Aconitum napellus;arnica montana;atropa bella-donna;bryonia alba;cinchona pubescens;drosera rotundifolia;eucalyptus globulus;eupatorium perfoliatum;gelsemium sempervirens;polygala senega	1 (1.4)	0	1 (0.7)
RETINOIDS FOR TREATMENT OF ACNE	1 (1.4)	0	1 (0.7)
Isotretinoin	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
SALICYLIC ACID PREPARATIONS	1 (1.4)	0	1 (0.7)
Glycerol;hyaluronate sodium;lactic acid;oryza sativa starch;salicylic acid;urea;vitellaria paradoxa subsp. paradoxa oil	1 (1.4)	0	1 (0.7)
SILICONE PRODUCTS	1 (1.4)	0	1 (0.7)
Dimeticone	1 (1.4)	0	1 (0.7)
STREPTOGRAMINS	1 (1.4)	0	1 (0.7)
Pristinamycin	1 (1.4)	0	1 (0.7)
SUBSTITUTED ETHYLENE DIAMINES	1 (1.4)	0	1 (0.7)
Chloropyramine	1 (1.4)	0	1 (0.7)
SULFONAMIDES	0	1 (1.4)	1 (0.7)
Chlorphenamine maleate;chondroitin sulfate sodium;sodium gualenate hydrate;sulfamethoxazole	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in

treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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Study Code: D134BC00001 Phase III
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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)	 Total (N=145)
SYMPATHOMIMETICS	0	1 (1.4)	1 (0.7)
Pseudoephedrine hydrochloride	0	1 (1.4)	1 (0.7)
SYMPATHOMIMETICS, COMBINATIONS EXCL. CORTICOSTEROIDS	0	1 (1.4)	1 (0.7)
Dexpanthenol;xylometazoline hydrochloride	0	1 (1.4)	1 (0.7)
TRIAZOLE AND TETRAZOLE DERIVATIVES	1 (1.4)	0	1 (0.7)
Fluconazole	1 (1.4)	0	1 (0.7)
VITAMIN A, PLAIN	0	1 (1.4)	1 (0.7)
Retinol	0	1 (1.4)	1 (0.7)
VITAMIN K AND OTHER HEMOSTATICS	0	1 (1.4)	1 (0.7)
Vitamin k and other hemostatics	0	1 (1.4)	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy,

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Table 14.1.6.2 Allowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
VITAMINS WITH MINERALS	0	1 (1.4)	1 (0.7)
Vitamins with minerals	0	1 (1.4)	1 (0.7)
VITAMINS, OTHER COMBINATIONS	1 (1.4)	0	1 (0.7)
Cystine;pyridoxine hydrochloride	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

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2.4.2 Nicht erlaubte Begleitmedikation in der Studie KOMET

Study Code: D134BC00001 Phase III
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Table 14.1.6.4 Disallowed concomitant medications during the randomised period (Full analysis set)

	Number (%) of subjects		
ATC classification Generic term	Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
Number of subjects with disallowed concomitant medication	6 (8.5)	4 (5.4)	10 (6.9)
PROTON PUMP INHIBITORS	2 (2.8)	3 (4.1)	5 (3.4)
Omeprazole	1 (1.4)	2 (2.7)	3 (2.1)
Esomeprazole	1 (1.4)	0	1 (0.7)
Omeprazole sodium	0	1 (1.4)	1 (0.7)
OTHER ANALGESICS AND ANTIPYRETICS	1 (1.4)	1 (1.4)	2 (1.4)
Cannabidiol	1 (1.4)	1 (1.4)	2 (1.4)
IMIDAZOLE DERIVATIVES	1 (1.4)	0	1 (0.7)
Metronidazole	1 (1.4)	0	1 (0.7)
OTHER ANXIOLYTICS	1 (1.4)	0	1 (0.7)
Fluoxetine	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date

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until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent
therapy,
or data cut-off.
Program: S:\AZ\Selumetinib\KOMET\PSC_U\Prog\Output\cm203.sas                                    Executed : 2024-11-12T151250
```

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
Table 14.1.6.4 Disallowed concomitant medications during the randomised period (Full analysis set)

ATC classification Generic term	Number (%) of subjects Selumetinib 25 mg/m2 BID (N=71)	Placebo (N=74)	Total (N=145)
OTHER CENTRALLY ACTING AGENTS	1 (1.4)	0	1 (0.7)
Clonixin lysinate;cyclobenzaprine hydrochloride	1 (1.4)	0	1 (0.7)

A subject can have one or more generic terms reported under a given ATC text. Concomitant medication during the randomised period is any medication started before or after first dose of study intervention that is taken during the randomised safety period. Table is sorted by most frequent ATC classification followed by generic drug name. WHODrug Global World Health Organization Global Drug Dictionary B3-format Sep 2023. ATC Anatomical Therapeutic Chemical. N Number of subjects in treatment group. Full analysis set - subjects randomised to study intervention. Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

Program: S:\AZ\Selumetinib\KOMET\PSC_U\Prog\Output\cm203.sas Executed : 2024-11-12T151250