Dossier zur Nutzenbewertung gemäß § 35a SGB V

Selumetinib (Koselugo®)

Alexion Pharma Germany GmbH

Modul 4 B, Anhang 4-H

Behandlung von symptomatischen, inoperablen plexiformen Neurofibromen bei Erwachsenen mit Neurofibromatose Typ 1

Subgruppenanalysen

Stand: 14.11.2025

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Anhang 4-H: Subgruppenanalysen

Anhang 4-H.1: Morbidität

Anhang 4-H.1.1: Volumenänderung der Zielläsion

Anhang 4-H.1.1.1: Volumenänderung der Zielläsion – Absolute Volumenänderung der Zielläsion im Vergleich zu Baseline – Zyklus 12, Tag 28 und über die randomisierte Phase

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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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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.
Program: t_pn_continuous_subgroup.sas Executed: 30SEP2025 10:52:21

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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.
Program: t_pn_continuous_subgroup.sas Executed: 30SEP2025 10:52:22

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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.
Program: t_pn_continuous_subgroup.sas Executed: 30SEP2025 10:52:11

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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

Anhang 4-H.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.
Program: t_pn_continuous_subgroup.sas Executed: 30SEP2025 10:51:46

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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.
Program: t_pn_continuous_subgroup.sas Executed: 30SEP2025 10:51:50

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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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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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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Study Code: D134BC00001 Phase III
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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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Anhang 4-H.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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Study Code: D134BC00001 Phase III
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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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Study Code: D134BC00001 Phase III

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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).
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:29

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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).
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:29

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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).
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:30

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:30

Study Code: D134BC00001 Phase III
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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:31

Study Code: D134BC00001 Phase III
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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:31

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:31

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:32

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:32

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:32

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:33

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:33

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:33

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:34

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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.
Program: t_pn_best_continuous_subgroup.sas Executed: 15SEP2025 15:15:34

Study Code: D134BC00001 Phase III
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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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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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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Study Code: D134BC00001 Phase III
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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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PSC_U Data Cut-Off 2024-08-05
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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Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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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Anhang 4-H.1.1.4: Volumenänderung der Zielläsion – Patienten mit einer Verringerung der Zielläsion um ≥ 20 % – Zyklus 12, Tag 28

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PSC_U Data Cut-Off 2024-08-05
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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PSC_U Data Cut-Off 2024-08-05
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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Anhang 4-H.1.2: Ansprechen

Anhang 4-H.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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Anhang 4-H.1.3: Schmerz anhand PAINS-pNF

Anhang 4-H.1.3.1: Schmerz anhand PAINS-pNF – chronischer Schmerz

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.3.2: Schmerz anhand PAINS-pNF – Schmerzspitze

Anhang 4-H.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.
Program: t_tte_subgrp_22.sas Executed: 09JUL2025 12:47:44

Anhang 4-H.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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Anhang 4-H.1.4: Schmerzlinderung chronischer Schmerzen

Anhang 4-H.1.4.1: Schmerzlinderung chronischer Schmerzen – Zeit bis zur erstmaligen Schmerzlinderung – Hauptanalyse

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.5: Schmerz anhand PGIC

Anhang 4-H.1.5.1: Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – chronischer Schmerz

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.5.2: Schmerz anhand PGIC 1 (Schmerzen seit der letzten Visite im Studienzentrum) – Schmerzspitze

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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.
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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.
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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.
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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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Anhang 4-H.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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Anhang 4-H.1.5.3: Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – chronischer Schmerz

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.5.4: Schmerz anhand PGIC 2 (Schmerzen seit Beginn der Studienmedikation) – Schmerzspitze

Anhang 4-H.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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Anhang 4-H.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.
Program: t_pro_binary_c12d28_subgrp_2.sas Executed: 18AUG2025 16:33:44

Anhang 4-H.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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Anhang 4-H.1.6: Schmerz anhand PGIS

Anhang 4-H.1.6.1: Schmerz anhand PGIS – chronischer Schmerz

Anhang 4-H.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

	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	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

						Comparison of treatment groups			
	Treatment group	n	Subjects 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	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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Anhang 4-H.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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Anhang 4-H.1.6.2: Schmerz anhand PGIS – Schmerzspitze

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.7: Schmerz anhand der Schmerzmedikation

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.8: Tägliche Funktionsfähigkeit anhand PII–pNF

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.9: Gesundheitszustand anhand EQ-5D VAS

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.1.10: Körperliche Funktionsfähigkeit anhand PROMIS

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.2: Gesundheitsbezogene Lebensqualität

Anhang 4-H.2.1: Gesundheitsbezogene Lebensqualität anhand PlexiQoL

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.2.2: Gesundheitsbezogene Lebensqualität anhand PedsQL

Anhang 4-H.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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Anhang 4-H.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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Anhang 4-H.3: Sicherheit

Anhang 4-H.3.1: Unerwünschte Ereignisse

Anhang 4-H.3.1.1: Unerwünschte Ereignisse – Jegliche UE

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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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Anhang 4-H.3.1.2: Unerwünschte Ereignisse – Schwere UE (CTCAE–Grad ≥ 3)

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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
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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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Anhang 4-H.3.1.3: Unerwünschte Ereignisse – Schwerwiegende UE

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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
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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:35:59

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:35:59

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:35:59

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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

Study Code: D134BC00001 Phase III
PSC_U Data Cut-Off 2024-08-05
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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:02

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:03

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:03

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:03

Anhang 4-H.3.1.4: Unerwünschte Ereignisse – Dauerhafter Therapieabbruch aufgrund von UE

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PSC_U Data Cut-Off 2024-08-05
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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:44

Study Code: D134BC00001 Phase III
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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:44

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PSC_U Data Cut-Off 2024-08-05
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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:34

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:34

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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
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:37

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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
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:37

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PSC_U Data Cut-Off 2024-08-05
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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PSC_U Data Cut-Off 2024-08-05
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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:43

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:43

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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.
Program: t_ae_summary_subgroup.sas Executed: 08SEP2025 17:36:43

Anhang 4-H.3.2: Unerwünschte Ereignisse nach SOC/PT

Anhang 4-H.3.2.1: Jegliche UE nach SOC/PT

Anhang 4-H.3.2.1.1: Jegliche Unerwünschte Ereignisse nach SOC/PT – Alter

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PSC_U Data Cut-Off 2024-08-05
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.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:19

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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.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:19

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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.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:19

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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.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:19

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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.
Program: t_ae_summary_socpt_subgrp.sas Executed: 16OCT2025 12:31:19

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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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Anhang 4-H.3.2.1.2: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.3: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.4: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.5: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.6: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.7: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.8: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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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Anhang 4-H.3.2.1.9: Jegliche Unerwünschte Ereignisse nach SOC/PT – 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.
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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: 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.
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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.
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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: 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.
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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: 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.
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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: 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.
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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: 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.
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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.
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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: 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.
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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.
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