Dossier zur Nutzenbewertung gemäß § 35a SGB V

Selumetinib (Koselugo®)

Alexion Pharma Germany GmbH

Anhang 4-G4

Studie KOMET
Finaler Datenschnitt vom 17. März 2025 –
weitere Auswertungen

Stand: 04.02.2026

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1 Endpunktkategorie Morbidität

1.1 Endpunkt Volumenänderung der Zielläsion

1.1.1 Volumenänderung der Zielläsion – Veränderung zu Baseline

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Table 14.2.1.2 Target PN volume (mL), actual value and change from baseline (Full analysis set)

		Absolute Values (ml)							
Treatment group	Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
Selumetinib 25 mg/m2 BID (N=71)	Baseline	71	836.26	2369.623	3.3	29.37	110.18	381.73	13578.4
	Cycle 4, Day 28	64	804.33	2257.425	3.0	25.82	89.41	343.46	12732.8
	Cycle 8, Day 28	60	901.69	2473.445	2.9	30.66	84.21	343.30	13167.1
	Cycle 12, Day 28	57	624.02	1917.782	3.0	32.35	92.63	295.08	12740.2
	Cycle 16, Day 28	52	419.66	1034.225	3.2	31.04	74.36	263.37	5056.4
	Cycle 20, Day 28	52	434.54	1089.756	3.2	27.48	59.78	269.00	5525.1
	Cycle 24, Day 28	50	428.70	1080.073	3.9	28.09	72.55	270.81	5920.3
	Cycle 30, Day 28	23	608.93	1349.232	3.9	41.15	136.60	361.10	6001.9
	Cycle 36, Day 28	5	265.61	399.227	17.1	54.23	69.15	221.61	966.0
	Cycle 42, Day 28	1	60.36	NC	60.4	60.36	60.36	60.36	60.4
	End of Treatment	16	2320.68	5386.254	3.6	16.50	159.73	902.68	19905.6

Percent change from baseline = (post-baseline value - baseline value) / (baseline value) * 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.1.2 Target PN volume (mL), actual value and change from baseline (Full analysis set)

		Change from baseline (ml)							
Treatment group	Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
Selumetinib 25 mg/m2 BID (N=71)	Baseline								
	Cycle 4, Day 28	64	-86.20	269.779	-1321.2	-23.69	-2.74	0.04	123.5
	Cycle 8, Day 28	60	-44.19	160.396	-641.4	-29.02	-5.32	-1.15	534.6
	Cycle 12, Day 28	57	-82.19	250.404	-1178.5	-22.21	-5.02	0.22	140.0
	Cycle 16, Day 28	52	-80.68	253.564	-1341.8	-32.94	-7.73	-0.44	95.4
	Cycle 20, Day 28	52	-68.12	220.487	-1368.1	-34.66	-7.81	-0.62	140.5
	Cycle 24, Day 28	50	-84.89	291.769	-1969.8	-39.51	-7.81	-0.59	63.7
	Cycle 30, Day 28	23	-54.71	125.103	-447.2	-83.71	-3.73	0.27	166.3
	Cycle 36, Day 28	5	-35.63	160.242	-303.7	-2.51	-1.98	0.39	129.7
	Cycle 42, Day 28	1	-11.31	NC	-11.3	-11.31	-11.31	-11.31	-11.3
	End of Treatment	16	268.94	1661.283	-1446.3	-9.83	-0.78	13.23	6327.3

Percent change from baseline = (post-baseline value - baseline value) / (baseline value) * 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.1.2 Target PN volume (mL), actual value and change from baseline (Full analysis set)

		% Change from baseline							
Treatment group	Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
Selumetinib 25 mg/m2 BID (N=71)	Baseline								
	Cycle 4, Day 28	64	-7.76	12.739	-32.7	-16.56	-9.88	0.01	28.5
	Cycle 8, Day 28	60	-8.81	15.785	-41.5	-17.89	-10.58	-4.26	47.6
	Cycle 12, Day 28	57	-9.41	21.710	-50.7	-19.40	-13.15	0.18	90.3
	Cycle 16, Day 28	52	-13.65	18.299	-58.1	-23.43	-15.00	-2.19	27.6
	Cycle 20, Day 28	52	-13.83	18.008	-59.0	-22.60	-12.00	-3.06	31.0
	Cycle 24, Day 28	50	-14.64	18.677	-56.0	-26.75	-13.93	-4.79	23.0
	Cycle 30, Day 28	23	-9.57	20.064	-48.1	-22.85	-13.50	4.41	48.6
	Cycle 36, Day 28	5	20.78	67.864	-23.9	-10.41	-3.50	0.72	141.0
	Cycle 42, Day 28	1	-15.78	NC	-15.8	-15.78	-15.78	-15.78	-15.8
	End of Treatment	16	1.22	16.266	-15.7	-11.03	-2.76	11.21	46.6

Percent change from baseline = (post-baseline value - baseline value) / (baseline value) * 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.1.2 Target PN volume (mL), actual value and change from baseline (Full analysis set)

		Absolute Values (ml)							
Treatment group	Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
Placebo / Selumetinib 25 mg/m2 BID (N=74)	Baseline	74	539.53	927.236	9.1	49.65	221.85	529.63	5621.9
	Cycle 4, Day 28	70	550.56	952.739	10.5	54.46	211.75	558.82	5598.8
	Cycle 8, Day 28	68	586.90	971.247	9.2	59.58	230.48	622.29	5568.8
	Cycle 12, Day 28	63	557.43	951.954	10.1	54.79	214.83	654.95	5733.4
	Cycle 16, Day 28	61	516.50	837.758	14.3	64.44	239.03	554.82	5004.6
	Cycle 20, Day 28	59	567.52	967.362	14.6	64.02	210.83	595.82	5773.0
	Cycle 24, Day 28	53	489.25	662.296	14.3	66.90	246.28	591.11	3246.2
	Cycle 30, Day 28	26	719.31	836.264	19.6	140.48	402.48	1117.36	3072.5
	Cycle 36, Day 28	9	392.77	591.152	15.4	40.34	73.79	409.52	1544.5
	Cycle 42, Day 28	2	271.94	265.269	84.4	84.37	271.94	459.51	459.5
	End of Treatment	10	477.34	857.333	4.5	30.38	236.52	396.99	2855.6

Percent change from baseline = (post-baseline value - baseline value) / (baseline value) * 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.1.2 Target PN volume (mL), actual value and change from baseline (Full analysis set)

		Change from baseline (ml)							
Treatment group	Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
Placebo / Selumetinib 25 mg/m2 BID (N=74)	Baseline								
	Cycle 4, Day 28	70	14.47	82.172	-174.4	-3.69	1.55	13.52	579.2
	Cycle 8, Day 28	68	13.74	119.731	-419.4	-10.23	1.33	19.55	566.4
	Cycle 12, Day 28	63	-6.23	97.892	-505.8	-14.19	0.00	19.14	314.0
	Cycle 16, Day 28	61	-70.62	155.851	-617.3	-66.04	-7.41	3.32	125.9
	Cycle 20, Day 28	59	-26.56	185.262	-570.9	-56.40	-6.45	14.26	822.8
	Cycle 24, Day 28	53	-54.16	194.834	-770.9	-50.81	-9.67	1.13	624.1
	Cycle 30, Day 28	26	-70.87	317.495	-944.7	-188.95	-28.09	23.03	930.7
	Cycle 36, Day 28	9	-33.59	195.134	-415.5	-10.12	-6.42	21.46	306.0
	Cycle 42, Day 28	2	-64.63	144.766	-167.0	-166.99	-64.63	37.74	37.7
	End of Treatment	10	116.85	299.753	-65.4	-4.65	7.95	60.85	952.7

Percent change from baseline = (post-baseline value - baseline value) / (baseline value) * 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.1.2 Target PN volume (mL), actual value and change from baseline (Full analysis set)

		% Change from baseline							
Treatment group	Timepoint	n	Mean	SD	Min	Q1	Median	Q3	Max
Placebo / Selumetinib 25 mg/m2 BID (N=74)	Baseline								
	Cycle 4, Day 28	70	3.29	9.263	-18.8	-2.17	2.29	10.03	38.6
	Cycle 8, Day 28	68	2.91	15.145	-31.0	-7.09	2.19	9.08	71.3
	Cycle 12, Day 28	63	-0.86	13.155	-42.2	-9.03	0.00	8.20	28.0
	Cycle 16, Day 28	61	-8.20	16.651	-44.0	-19.09	-9.21	3.27	29.5
	Cycle 20, Day 28	59	-4.20	27.063	-41.2	-20.33	-7.60	4.82	139.6
	Cycle 24, Day 28	53	-6.88	24.259	-45.9	-25.57	-9.23	1.72	55.7
	Cycle 30, Day 28	26	-5.47	28.924	-47.3	-24.99	-15.89	17.15	51.6
	Cycle 36, Day 28	9	-2.04	34.181	-39.7	-24.53	-18.77	28.22	58.3
	Cycle 42, Day 28	2	27.14	76.077	-26.7	-26.65	27.14	80.93	80.9
	End of Treatment	10	13.21	31.881	-50.9	-2.26	18.06	39.10	50.1

Percent change from baseline = (post-baseline value - baseline value) / (baseline value) * 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the protocolled visit day are selected for this summary, therefore unscheduled visits may be excluded. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated.
Full analysis set - subjects randomised to study intervention.
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1.1.2 Volumenänderung der Zielläsion – Beste erreichte prozentuale Volumenänderung der Zielläsion

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Table 14.2.9.8 Post-hoc - Best percentage change from baseline in target PN volume, summary statistics, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Best % change from baseline							
Treatment group	n	Mean	SD	Min	Q1	Median	Q3	Max
Selumetinib 25 mg/m2 BID (N=71)	65	-18.13	15.797	-59.0	-24.79	-16.91	-10.60	23.0

Best percentage change is the maximum reduction from baseline or the minimum increase from baseline in the absence of reduction. A negative change denotes a reduction in target PN size. Includes all scheduled and unscheduled assessments until the earliest of progression, death , start of subsequent treatment, or the last evaluable MRI assessment.
On-treatment MRI volumetric assessments 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. Max Maximum. Min Minimum. n Number of subjects in analysis. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Selumetinib full analysis set - subjects randomised to selumetinib.
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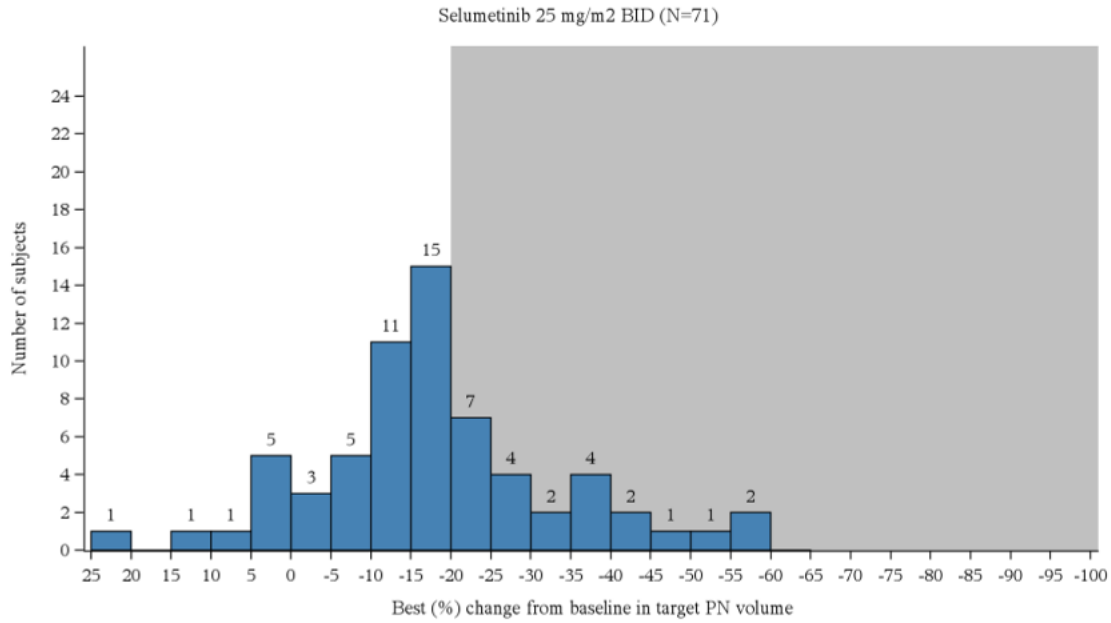
Figure 14.2.9.6 Target PN volume, best percentage change during the on-treatment MRI volumetric assessments period, histogram (Selumetinib full analysis set)



Best percentage change is derived as the maximum reduction from baseline or the minimum increase from baseline in the absence of reduction. The width of each histogram bar corresponds to a 5% PN volumetric change from baseline. The shaded area shows a best percentage change of less than -20% which indicates responders according to REiNS. Percentages greater than 100% are reported as 100%. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. Selumetinib full analysis set - subjects randomised to selumetinib. On-treatment MRI volumetric assessments period - from first dose until discontinuation or data cut-off (whichever occurs first). Scans performed during or soon after a prolonged study intervention interruption will not be excluded.
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1.2 Endpunkt Ansprechen

1.2.1 Ansprechen – Objektive Ansprechrate (ORR)

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Table 14.2.4.1 Objective response rate - single arm, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

Treatment group	N	Number (%) of subjects with response [a]	95% CI [b]
Selumetinib 25 mg/m2 BID	71	17 (23.9)	(14.6, 35.5)

[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. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib.
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.
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1.2.2 Ansprechen – Zeit bis zum Ansprechen (TTR)

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Table 14.2.8.1 Time to response, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Number (%) of subjects with a response [a]	17
Median time to response (months) [b]	6.93
95% CI for median time to response [b]	3.65 - 11.10
Response-free rate at 4 months (%) [b]	52.94
95% CI for response-free rate at 4 months [b]	27.62 - 73.03
Response-free rate at 8 months (%) [b]	41.18
95% CI for response-free rate at 8 months [b]	18.58 - 62.64
Response-free rate at 12 months (%) [b]	17.65
95% CI for response-free rate at 12 months [b]	4.35 - 38.30
Response-free rate at 16 months (%) [b]	5.88
95% CI for response-free rate at 16 months [b]	0.39 - 23.50

[a] Time to response (TTR) is the time from randomisation date until the date of first documented objective response (which is subsequently confirmed, cCR or cPR) as determined by ICR per REiNS criteria. [b] Calculated using the Kaplan-Meier technique. Only subjects who have achieved a cCR or a cPR are evaluated for TTR. cCR Confirmed complete response. CI Confidence interval. cPR Confirmed partial response. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. On-treatment MRI volumetric assessments 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. Selumetinib full analysis set - subjects randomised to selumetinib.
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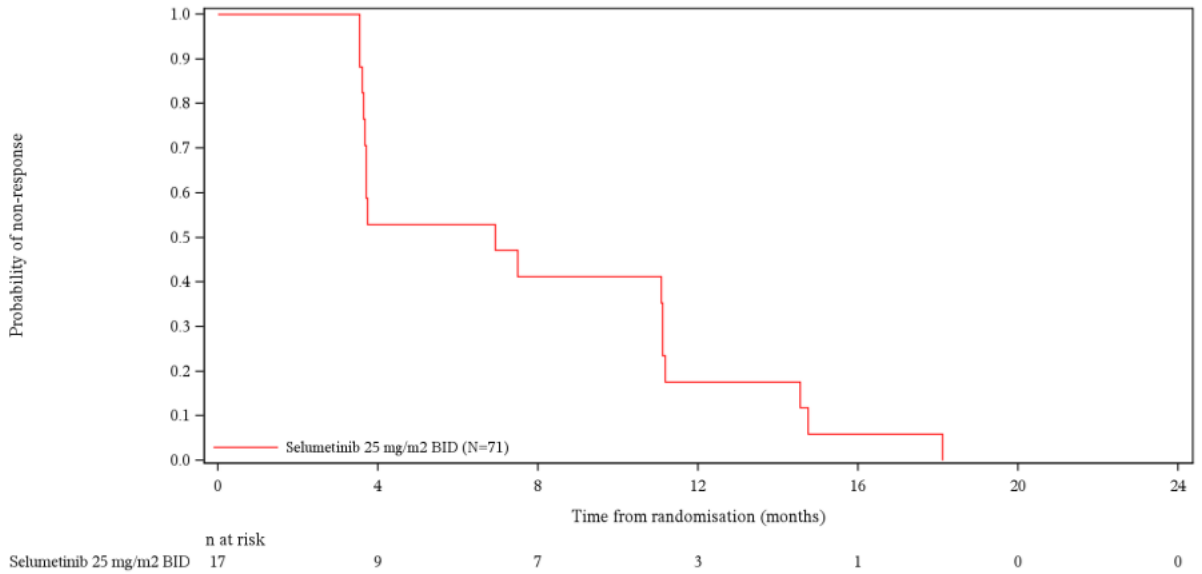
Figure 14.2.8.4 Time to response, Kaplan-Meier plot, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)



Time to response (TTR) is the time from randomisation date until the date of first documented objective response (which is subsequently confirmed, cCR or cPR) as determined by ICR per REiNS criteria. Only subjects who have achieved a cCR or a cPR are evaluated for TTR. cCR Confirmed complete response. cPR Confirmed partial response. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma.
REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.
On-treatment MRI volumetric assessments 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. Selumetinib full analysis set - subjects randomised to selumetinib.
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1.2.3 Ansprechen – Zeit bis zur Progression (TTP)

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Table 14.2.7.2 Time to progression, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Total events, n (%) [a]	10 (14.1)
REiNS progression	10 (14.1)
Censored subjects, n (%)	61 (85.9)
Median time to progression (months) [b]	NC
95% CI for median time to progression [b]	NC - NC
Progression free rate at 4 months (%) [b]	98.36
95% CI for progression free rate at 4 months [b]	88.93 - 99.77
Progression free rate at 8 months (%) [b]	93.39
95% CI for progression free rate at 8 months [b]	83.33 - 97.47
Progression free rate at 12 months (%) [b]	89.79
95% CI for progression free rate at 12 months [b]	78.66 - 95.29

[a] Time to progression (TTP) is the time from randomisation date until the date of first documented objective disease progression by ICR per REiNS criteria, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. [b] Calculated using the Kaplan-Meier technique. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib. 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.
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Table 14.2.7.2 Time to progression, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Progression free rate at 16 months (%) [b]	87.92
95% CI for progression free rate at 16 months [b]	76.28 - 94.06
Progression free rate at 20 months (%) [b]	87.92
95% CI for progression free rate at 20 months [b]	76.28 - 94.06
Progression free rate at 24 months (%) [b]	80.30
95% CI for progression free rate at 24 months [b]	65.73 - 89.16
Progression free rate at 30 months (%) [b]	80.30
95% CI for progression free rate at 30 months [b]	65.73 - 89.16
Progression free rate at 36 months (%) [b]	80.30
95% CI for progression free rate at 36 months [b]	65.73 - 89.16

[a] Time to progression (TTP) is the time from randomisation date until the date of first documented objective disease progression by ICR per REiNS criteria, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. [b] Calculated using the Kaplan-Meier technique. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib. 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.
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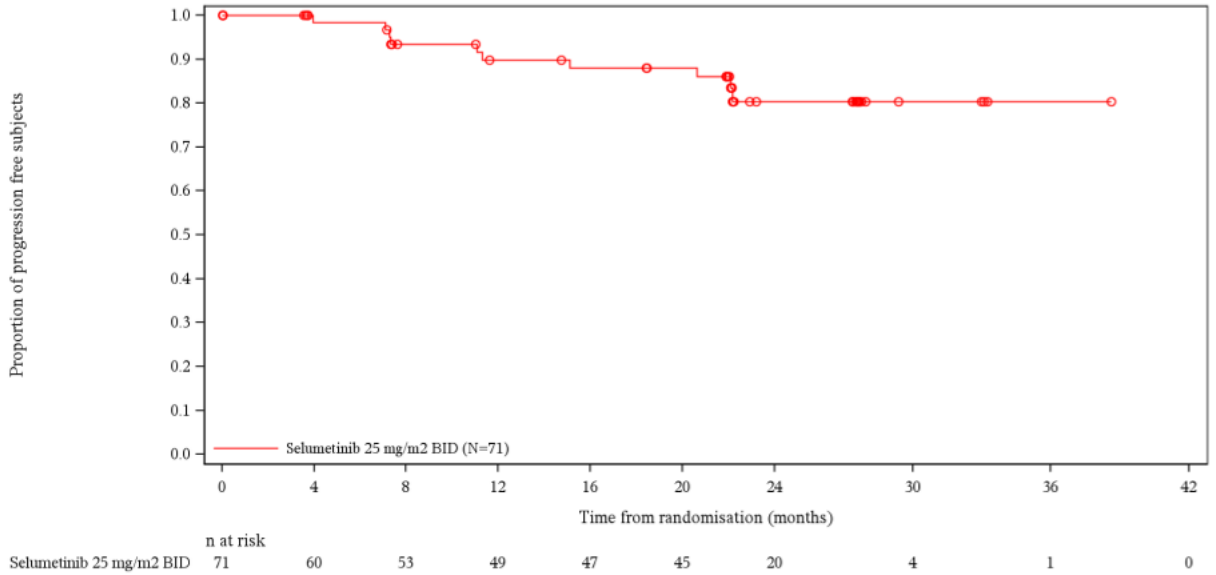
Figure 14.2.7.1 Time to progression, Kaplan-Meier plot, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)



Circle indicates a censored observation. Time to progression (TTP) is the time from randomisation date until the date of first documented objective disease progression by ICR per REiNS criteria, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib.
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.
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1.2.4 Ansprechen – Progressionsfreies Überleben (PFS)

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Final DCO PSC
Table 14.2.6.2 Progression free survival, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Total events, n (%) [a]	10 (14.1)
REiNS progression	10 (14.1)
Death in absence of REiNS progression	0
Censored subjects, n (%)	61 (85.9)
Median progression free survival (months) [b]	NC
95% CI for median progression free survival [b]	NC - NC
Progression free survival rate at 4 months (%) [b]	98.36
95% CI for progression free survival rate at 4 months [b]	88.93 - 99.77
Progression free survival rate at 8 months (%) [b]	93.39
95% CI for progression free survival rate at 8 months [b]	83.33 - 97.47
Progression free survival rate at 12 months (%) [b]	89.79
95% CI for progression free survival rate at 12 months [b]	78.66 - 95.29

[a] Progression free survival (PFS) is the time from randomisation date until the date of progression by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. [b] Calculated using the Kaplan-Meier technique. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib. 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.
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Final DCO PSC
Table 14.2.6.2 Progression free survival, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Progression free survival rate at 16 months (%) [b]	87.92
95% CI for progression free survival rate at 16 months [b]	76.28 - 94.06
Progression free survival rate at 20 months (%) [b]	87.92
95% CI for progression free survival rate at 20 months [b]	76.28 - 94.06
Progression free survival rate at 24 months (%) [b]	80.30
95% CI for progression free survival rate at 24 months [b]	65.73 - 89.16
Progression free survival rate at 30 months (%) [b]	80.30
95% CI for progression free survival rate at 30 months [b]	65.73 - 89.16
Progression free survival rate at 36 months (%) [b]	80.30
95% CI for progression free survival rate at 36 months [b]	65.73 - 89.16

[a] Progression free survival (PFS) is the time from randomisation date until the date of progression by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. [b] Calculated using the Kaplan-Meier technique. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib. 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.
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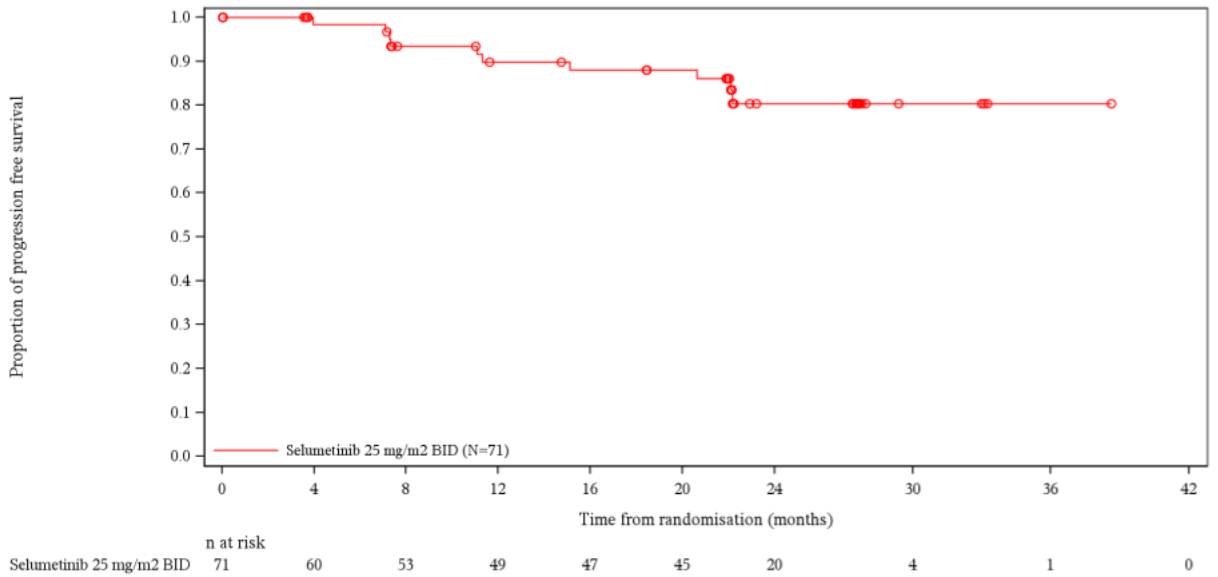
Figure 14.2.6.1 Progression free survival, Kaplan-Meier plot, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)



Circle indicates a censored observation. Progression free survival (PFS) is the time from randomisation date until the date of progression by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. PN Plexiform Neurofibroma. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. Selumetinib full analysis set - subjects randomised to selumetinib. 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.
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1.2.5 Ansprechen – Bestes objektives Ansprechen (BOR)

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Table 14.2.4.5 Best objective response - single arm, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Number (%) of subjects
Best objective response	Selumetinib 25 mg/m2 BID (N=71)
Confirmed complete response	0
Confirmed partial response	17 (23.9)
Stable disease	47 (66.2)
Unconfirmed complete response	0
Unconfirmed partial response	6 (8.5)
Stable disease	41 (57.7)
Progressive disease	1 (1.4)
Not evaluable	6 (8.5)

Best objective response is the best response a subject had following the start of intervention, but prior to starting any subsequent NF1 PN therapy and up to and including progression or the last evaluable MRI assessment in the absence of progression. MRI Magnetic resonance imaging. N Number of subjects in treatment group. NF1 Neurofibromatosis type 1. PN Plexiform Neurofibroma. Selumetinib full analysis set - subjects randomised to selumetinib.
On-treatment MRI volumetric assessments 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.
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1.2.6 Ansprechen – Dauer des Ansprechens (DOR)

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Table 14.2.5.2 Duration of response, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Subjects with objective response	17
Number of responders who subsequently progressed or died	3
Duration of response from onset of response (months) [a] [b]	
25th percentile	18.4
Median	NC
95% CI for median duration of response	11.50 - NC
75th percentile	NC
Number and percentage remaining in response n (%)	
>= 6 months	17 (100)
>= 8 months	16 (94.1)
>= 12 months	10 (58.8)
>= 16 months	8 (47.1)
>= 20 months	3 (17.6)
>= 24 months	1 (5.9)

[a] Duration of response (DoR) is the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression as assessed by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. [b] Calculated using the Kaplan-Meier technique. Only includes subjects who have a confirmed complete response or a confirmed partial response. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. NC Not calculated.
Selumetinib full analysis set - subjects randomised to selumetinib.
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Table 14.2.5.2 Duration of response, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Estimated percentage remaining in response [b]	
>= 6 months (95% CI)	100.0 (100.0 - 100.0)
>= 8 months (95% CI)	100.0 (100.0 - 100.0)
>= 12 months (95% CI)	83.9 (49.4 - 95.7)
>= 16 months (95% CI)	83.9 (49.4 - 95.7)
>= 20 months (95% CI)	69.9 (30.1 - 89.9)
>= 24 months (95% CI)	69.9 (30.1 - 89.9)

[a] Duration of response (DoR) is the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression as assessed by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. [b] Calculated using the Kaplan-Meier technique. Only includes subjects who have a confirmed complete response or a confirmed partial response. CI Confidence interval. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. NC Not calculated.
Selumetinib full analysis set - subjects randomised to selumetinib.
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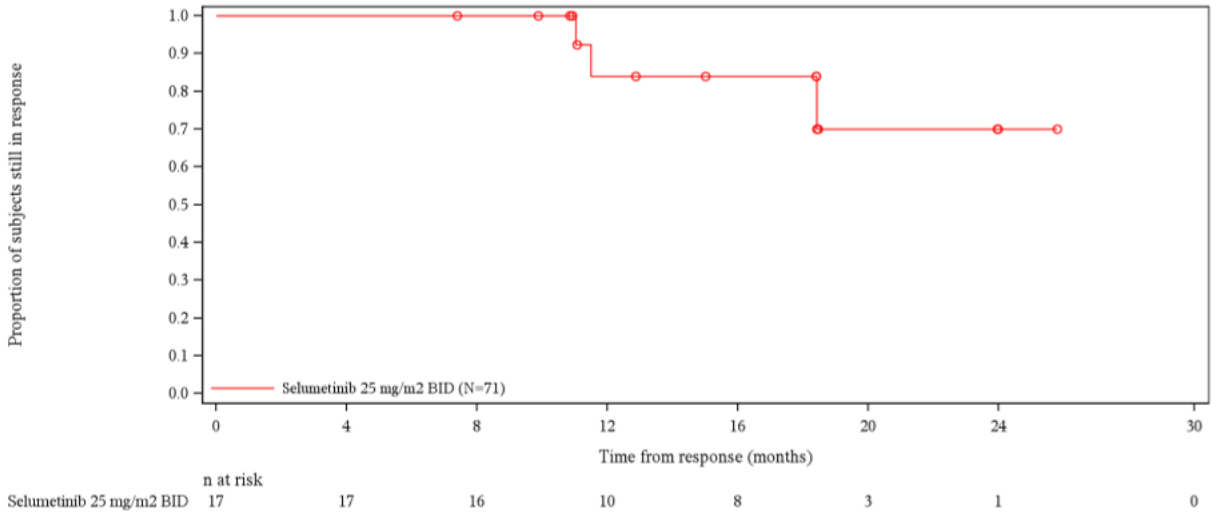
Final DCO PSC
Figure 14.2.5.1 Duration of response, Kaplan-Meier plot, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)



Circle indicates a censored observation. Duration of response (DoR) is the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression as assessed by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits. Only includes subjects who have a confirmed complete response or a confirmed partial response. ICR Independent Central Review. MRI Magnetic resonance imaging. N Number of subjects in treatment group. REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis. 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. Selumetinib full analysis set - subjects randomised to selumetinib.
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1.3 Endpunkt Schmerz

1.3.1 Schmerz anhand PAINS-pNF – chronischer Schmerz – Veränderung zu Baseline

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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	71		74	
	Mean	4.179		4.327	
	SD	2.5161		2.7085	
	Min	0.00		0.00	
	Q1	2.542		1.682	
	Median	4.185		4.433	
	Q3	5.708		6.722	
	Max	9.76		9.00	
Cycle 1	n	70	70	74	74
	Mean	3.690	-0.503	4.042	-0.286
	SD	2.5353	0.7778	2.8048	1.1158
	Min	0.00	-2.25	0.00	-4.93
	Q1	1.714	-0.982	1.607	-0.575
	Median	3.510	-0.342	4.161	-0.059
	Q3	5.357	0.000	6.429	0.179
	Max	10.00	1.32	9.93	1.73

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 2	n	69	69	74	74
	Mean	3.451	-0.704	3.811	-0.517
	SD	2.5538	1.0798	2.7623	1.5921
	Min	0.00	-4.31	0.00	-7.54
	Q1	1.321	-1.280	1.536	-0.671
	Median	3.179	-0.489	4.089	-0.217
	Q3	4.714	0.000	5.750	0.111
	Max	10.00	2.48	10.00	4.00
Cycle 3	n	67	67	74	74
	Mean	3.318	-0.923	3.758	-0.570
	SD	2.5312	1.3021	2.7512	1.6413
	Min	0.00	-4.61	0.00	-7.54
	Q1	1.222	-1.708	1.250	-0.929
	Median	3.286	-0.545	3.892	-0.271
	Q3	4.464	0.000	5.393	0.111
	Max	10.00	2.09	10.00	2.72

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 4	n	66	66	71	71
	Mean	3.122	-1.144	3.598	-0.647
	SD	2.4055	1.4540	2.7842	1.7750
	Min	0.00	-5.89	0.00	-7.54
	Q1	1.036	-2.137	1.037	-0.958
	Median	3.018	-0.775	3.714	-0.268
	Q3	4.391	0.000	5.214	0.169
	Max	10.00	1.67	10.00	2.79
Cycle 5	n	65	65	70	70
	Mean	3.135	-1.178	3.360	-0.830
	SD	2.3667	1.6300	2.7396	1.8231
	Min	0.00	-7.50	0.00	-7.54
	Q1	1.250	-2.071	1.037	-1.050
	Median	3.000	-0.833	3.000	-0.350
	Q3	4.600	0.000	4.964	0.000
	Max	10.00	2.12	10.00	3.03

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 6	n	64	64	69	69
	Mean	3.011	-1.245	3.381	-0.859
	SD	2.3383	1.5707	2.7326	1.8223
	Min	0.00	-6.68	0.00	-7.54
	Q1	1.072	-2.402	1.214	-1.150
	Median	2.782	-0.936	3.000	-0.497
	Q3	4.222	0.000	5.000	0.000
	Max	10.00	1.71	10.00	2.79
Cycle 7	n	61	61	69	69
	Mean	2.786	-1.512	3.359	-0.881
	SD	2.3533	1.6119	2.7433	1.9032
	Min	0.00	-6.93	0.00	-7.54
	Q1	1.000	-2.610	1.000	-1.250
	Median	2.296	-1.190	3.000	-0.461
	Q3	4.192	-0.046	5.000	0.015
	Max	10.00	0.83	10.00	3.70

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 8	n	62	62	69	69
	Mean	2.958	-1.352	3.347	-0.908
	SD	2.4545	1.7407	2.7444	2.0010
	Min	0.00	-6.68	0.00	-7.54
	Q1	1.000	-2.381	1.000	-1.314
	Median	2.848	-1.127	3.000	-0.427
	Q3	4.222	0.000	5.107	0.153
	Max	10.00	2.61	10.00	3.54
Cycle 9	n	62	62	68	68
	Mean	2.820	-1.405	3.394	-0.802
	SD	2.3541	1.7149	2.6930	1.8963
	Min	0.00	-7.00	0.00	-7.54
	Q1	1.000	-2.087	1.000	-1.306
	Median	2.537	-0.989	3.095	-0.506
	Q3	3.889	-0.009	5.071	0.083
	Max	10.00	2.32	10.00	3.66

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 10	n	62	62	67	67
	Mean	2.843	-1.411	3.198	-0.947
	SD	2.3897	1.7356	2.6424	1.9354
	Min	0.00	-7.68	0.00	-7.54
	Q1	1.000	-2.369	0.214	-1.436
	Median	2.786	-1.136	3.074	-0.627
	Q3	4.077	0.000	4.778	0.000
	Max	10.00	2.18	10.00	4.11
Cycle 11	n	58	58	66	66
	Mean	2.595	-1.584	3.164	-0.952
	SD	2.3224	1.8356	2.6888	1.9277
	Min	0.00	-7.11	0.00	-7.54
	Q1	0.810	-3.043	0.148	-1.460
	Median	2.076	-1.163	2.981	-0.410
	Q3	3.714	-0.224	4.714	0.021
	Max	10.00	2.46	10.00	4.07

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 12	n	59	59	65	65
	Mean	2.728	-1.547	3.121	-0.909
	SD	2.3561	1.9227	2.5993	1.9670
	Min	0.00	-7.54	0.00	-7.54
	Q1	1.000	-2.594	0.077	-1.440
	Median	2.357	-1.148	3.000	-0.302
	Q3	3.857	-0.031	4.815	0.000
	Max	10.00	2.91	9.78	3.92
Cycle 13	n	59	59	61	61
	Mean	2.772	-1.511	2.844	-1.119
	SD	2.3703	1.8897	2.4614	2.0540
	Min	0.00	-7.68	0.00	-7.54
	Q1	1.000	-2.735	0.179	-1.476
	Median	2.455	-1.030	2.889	-0.714
	Q3	3.857	-0.067	4.500	-0.026
	Max	10.00	2.34	9.77	3.91

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 14	n	55	55	60	60
	Mean	2.711	-1.556	2.736	-1.293
	SD	2.3589	1.8993	2.3747	2.0761
	Min	0.00	-7.86	0.00	-7.54
	Q1	0.929	-2.402	0.233	-1.804
	Median	2.130	-1.000	3.000	-0.740
	Q3	4.357	-0.005	4.128	-0.052
	Max	10.00	2.59	9.93	4.07
Cycle 15	n	54	54	60	60
	Mean	2.741	-1.549	2.666	-1.363
	SD	2.4766	1.9473	2.2705	2.0797
	Min	0.00	-7.46	0.00	-7.54
	Q1	1.000	-2.958	0.089	-1.856
	Median	2.189	-1.170	3.000	-0.885
	Q3	3.893	-0.036	4.164	-0.074
	Max	10.00	2.30	10.00	4.14

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 16	n	54	54	61	61
	Mean	2.522	-1.611	2.655	-1.454
	SD	2.2809	1.9000	2.4626	2.2028
	Min	0.00	-7.34	0.00	-7.77
	Q1	0.444	-3.071	0.074	-2.000
	Median	2.129	-1.000	2.957	-0.932
	Q3	3.529	-0.048	4.000	-0.077
	Max	10.00	1.49	10.00	4.14
Cycle 17	n	51	51	59	59
	Mean	2.609	-1.617	2.480	-1.516
	SD	2.3084	1.9710	2.3459	2.3073
	Min	0.00	-7.68	0.00	-7.54
	Q1	0.143	-3.071	0.040	-2.476
	Median	2.214	-1.148	2.480	-0.750
	Q3	3.893	0.000	4.000	-0.071
	Max	10.00	1.41	10.00	4.14

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 18	n	51	51	59	59
	Mean	2.526	-1.593	2.345	-1.651
	SD	2.2608	2.0039	2.2880	2.3077
	Min	0.00	-7.93	0.00	-7.54
	Q1	0.391	-2.940	0.000	-2.941
	Median	2.444	-1.148	2.143	-0.901
	Q3	3.357	0.000	4.000	-0.071
	Max	10.00	1.91	10.00	4.14
Cycle 19	n	49	49	55	55
	Mean	2.723	-1.466	2.221	-1.849
	SD	2.4504	2.0344	2.3619	2.4327
	Min	0.00	-7.82	0.00	-7.85
	Q1	0.926	-2.671	0.000	-3.431
	Median	2.632	-1.111	1.786	-1.038
	Q3	3.435	-0.049	4.000	-0.077
	Max	10.00	3.41	9.96	4.10

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 20	n	50	50	57	57
	Mean	2.657	-1.431	2.364	-1.778
	SD	2.4031	2.1900	2.5359	2.4530
	Min	0.00	-7.71	0.00	-7.85
	Q1	0.875	-2.708	0.000	-2.994
	Median	2.368	-1.074	2.037	-1.067
	Q3	3.893	0.000	3.870	-0.115
	Max	10.00	4.16	10.00	4.14
Cycle 21	n	47	47	54	54
	Mean	2.668	-1.437	2.175	-1.879
	SD	2.3512	2.1244	2.3048	2.3750
	Min	0.00	-7.82	0.00	-7.54
	Q1	0.929	-2.745	0.000	-3.544
	Median	2.500	-1.000	1.571	-1.271
	Q3	3.821	0.000	3.619	-0.077
	Max	10.00	4.45	9.89	4.03

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 22	n	46	46	55	55
	Mean	2.604	-1.525	2.309	-1.832
	SD	2.2281	2.0913	2.5629	2.4766
	Min	0.00	-8.11	0.00	-7.54
	Q1	1.000	-2.708	0.071	-3.726
	Median	2.609	-0.820	1.393	-1.067
	Q3	3.893	-0.036	3.630	-0.071
	Max	10.00	4.48	10.00	4.14
Cycle 23	n	46	46	53	53
	Mean	2.535	-1.468	1.979	-1.934
	SD	2.2194	2.2561	2.2667	2.5402
	Min	0.00	-8.56	0.00	-8.00
	Q1	0.185	-3.071	0.038	-3.667
	Median	2.584	-0.766	1.074	-1.294
	Q3	3.370	-0.036	3.111	-0.071
	Max	10.00	4.88	10.00	4.14

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 24	n	46	46	52	52
	Mean	2.850	-1.251	1.846	-2.021
	SD	2.4805	2.2870	2.1782	2.4867
	Min	0.00	-8.43	0.00	-7.85
	Q1	0.321	-2.894	0.000	-3.941
	Median	2.679	-0.716	1.196	-1.266
	Q3	4.560	0.000	3.019	-0.096
	Max	9.71	4.91	10.00	4.14
Cycle 25	n	42	42	44	44
	Mean	2.554	-1.499	1.830	-2.234
	SD	2.4371	2.2135	2.0198	2.4775
	Min	0.00	-8.67	0.00	-7.86
	Q1	0.077	-2.923	0.000	-4.295
	Median	2.071	-1.071	1.090	-1.162
	Q3	4.179	0.000	3.229	-0.256
	Max	10.00	4.91	7.04	1.42

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 26	n	34	34	41	41
	Mean	2.663	-1.167	1.669	-2.286
	SD	2.5744	1.9036	1.8675	2.5743
	Min	0.00	-5.01	0.00	-8.00
	Q1	0.074	-2.231	0.000	-4.400
	Median	2.205	-0.774	1.000	-1.292
	Q3	4.520	0.000	3.000	-0.077
	Max	10.00	4.59	6.22	1.60
Cycle 27	n	30	30	38	38
	Mean	2.340	-1.304	1.844	-2.015
	SD	2.5764	2.0831	2.3522	2.5674
	Min	0.00	-5.09	0.00	-8.61
	Q1	0.000	-3.005	0.000	-4.190
	Median	1.769	-0.754	1.024	-1.019
	Q3	4.786	0.000	3.250	-0.071
	Max	10.00	4.20	10.00	1.43

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 28	n	28	28	34	34
	Mean	2.346	-1.079	1.604	-2.022
	SD	2.5304	1.9947	2.2943	2.6249
	Min	0.00	-5.09	0.00	-8.96
	Q1	0.000	-2.595	0.000	-4.190
	Median	1.921	-0.566	0.236	-1.037
	Q3	3.856	0.000	3.000	-0.115
	Max	10.00	4.23	10.00	1.71
Cycle 29	n	27	27	30	30
	Mean	2.139	-1.106	1.154	-1.947
	SD	2.5907	1.9147	1.5167	2.4427
	Min	0.00	-4.76	0.00	-8.96
	Q1	0.000	-2.267	0.000	-3.659
	Median	1.000	-0.772	0.091	-1.037
	Q3	3.107	0.000	2.214	-0.231
	Max	10.00	4.20	5.21	1.38

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 30	n	23	23	26	26
	Mean	2.282	-0.800	0.834	-1.818
	SD	2.6980	1.7991	1.2913	2.5722
	Min	0.00	-4.91	0.00	-9.00
	Q1	0.038	-1.670	0.000	-2.889
	Median	1.000	-0.134	0.036	-0.796
	Q3	4.571	0.000	1.000	-0.115
	Max	10.00	3.88	5.21	1.46
Cycle 31	n	16	16	22	22
	Mean	2.696	-0.931	0.929	-1.565
	SD	3.1397	2.2074	1.3637	1.7678
	Min	0.00	-4.91	0.00	-5.04
	Q1	0.000	-1.615	0.000	-2.926
	Median	1.500	-0.784	0.179	-1.125
	Q3	4.806	-0.018	2.045	-0.071
	Max	10.00	4.66	5.21	1.05

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 32	n	12	12	17	17
	Mean	2.457	-1.186	1.086	-1.516
	SD	3.1951	1.7277	1.4880	1.8642
	Min	0.00	-4.59	0.00	-6.04
	Q1	0.038	-1.615	0.000	-1.736
	Median	1.000	-0.590	0.250	-1.292
	Q3	4.031	-0.018	1.300	-0.071
	Max	10.00	0.53	5.04	0.72
Cycle 33	n	7	7	11	11
	Mean	3.324	-1.221	1.238	-1.861
	SD	3.6407	1.7445	1.7179	2.2168
	Min	0.00	-4.63	0.00	-6.18
	Q1	0.038	-2.195	0.000	-4.175
	Median	2.929	-0.818	0.292	-1.292
	Q3	6.071	0.159	3.000	-0.071
	Max	10.00	0.24	5.11	0.86

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 34	n	7	7	9	9
	Mean	3.406	-1.140	1.710	-1.926
	SD	3.6476	1.7640	1.7295	2.2477
	Min	0.00	-4.63	0.00	-5.68
	Q1	0.036	-2.124	0.417	-4.050
	Median	3.107	-0.818	1.286	-1.500
	Q3	6.143	0.240	3.000	-0.333
	Max	10.00	0.34	5.22	0.82
Cycle 35	n	7	7	9	9
	Mean	3.360	-1.186	1.732	-1.904
	SD	3.6249	1.7419	1.6673	1.9876
	Min	0.00	-4.57	0.00	-5.00
	Q1	0.100	-2.231	0.800	-3.667
	Median	3.036	-0.818	1.000	-1.544
	Q3	6.036	0.240	2.500	-0.333
	Max	10.00	0.27	5.18	0.32

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 36	n	6	6	9	9
	Mean	3.870	-0.655	1.747	-1.889
	SD	3.6470	1.0076	1.5831	1.9974
	Min	0.00	-2.27	0.00	-5.21
	Q1	1.000	-1.316	0.923	-3.544
	Median	3.111	-0.409	1.577	-1.223
	Q3	6.000	0.231	2.259	-0.333
	Max	10.00	0.24	5.04	0.08
Cycle 37	n	6	6	9	9
	Mean	3.826	-0.700	1.795	-1.841
	SD	3.6723	0.9548	1.8127	2.0379
	Min	0.00	-2.20	0.00	-5.79
	Q1	1.000	-1.396	0.571	-2.229
	Median	2.942	-0.423	1.357	-0.972
	Q3	6.071	0.000	2.370	-0.333
	Max	10.00	0.24	5.75	0.00

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 38	n	5	5	9	9
	Mean	4.637	-0.793	1.766	-1.870
	SD	3.4875	1.0591	1.6229	1.9809
	Min	1.00	-2.27	0.00	-5.29
	Q1	2.963	-1.316	1.000	-3.383
	Median	3.222	-0.818	1.630	-1.170
	Q3	6.000	0.194	2.071	-0.333
	Max	10.00	0.24	5.25	0.00
Cycle 39	n	4	4	7	7
	Mean	5.509	-0.824	1.872	-1.924
	SD	3.3090	1.2144	1.9443	2.2282
	Min	2.89	-2.27	0.00	-5.61
	Q1	3.019	-1.828	0.000	-4.400
	Median	4.574	-0.635	1.536	-1.187
	Q3	8.000	0.180	3.000	-0.105
	Max	10.00	0.24	5.54	0.00

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 40	n	3	3	5	5
	Mean	6.392	-1.129	2.406	-2.282
	SD	3.4585	1.2457	1.9362	2.5145
	Min	3.11	-2.20	0.00	-5.46
	Q1	3.105	-2.195	1.679	-4.400
	Median	6.071	-1.433	2.080	-1.449
	Q3	10.000	0.240	3.000	-0.096
	Max	10.00	0.24	5.27	0.00
Cycle 41	n	2	2	3	3
	Mean	8.018	-0.995	1.426	-3.422
	SD	2.8032	1.7472	1.5055	3.0525
	Min	6.04	-2.23	0.00	-5.87
	Q1	6.036	-2.231	0.000	-5.865
	Median	8.018	-0.995	1.278	-4.400
	Q3	10.000	0.240	3.000	0.000
	Max	10.00	0.24	3.00	0.00

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.2.7 PAINS-pNF chronic target PN pain intensity scores: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 42	n	1	1	2	2
	Mean	6.071	-2.195	1.500	-2.200
	SD	NC	NC	2.1213	3.1113
	Min	6.07	-2.20	0.00	-4.40
	Q1	6.071	-2.195	0.000	-4.400
	Median	6.071	-2.195	1.500	-2.200
	Q3	6.071	-2.195	3.000	0.000
	Max	6.07	-2.20	3.00	0.00

Baseline score is derived if at least 4 daily pain scores are non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score is derived if at least 4 daily pain scores are non-missing in at least 3 non-overlapping 7-day periods. A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. NC Not calculated. Full analysis set - subjects randomised to study intervention.
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1.3.2 Schmerz anhand PAINS-pNF – Schmerzspitze – Veränderung zu Baseline

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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	71		74	
	Mean	6.592		6.338	
	SD	2.6218		2.9990	
	Min	0.00		0.00	
	Q1	5.000		5.000	
	Median	7.000		7.000	
	Q3	9.000		9.000	
	Max	10.00		10.00	
Cycle 1	n	71	71	74	74
	Mean	5.972	-0.620	5.919	-0.419
	SD	2.7722	1.5979	3.0420	1.7673
	Min	0.00	-5.00	0.00	-6.00
	Q1	4.000	-1.000	4.000	-1.000
	Median	6.000	-1.000	7.000	0.000
	Q3	8.000	0.000	8.000	0.000
	Max	10.00	6.00	10.00	9.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 2	n	70	70	74	74
	Mean	5.243	-1.343	5.554	-0.784
	SD	2.9362	1.7684	3.0437	1.8377
	Min	0.00	-7.00	0.00	-8.00
	Q1	3.000	-2.000	4.000	-1.000
	Median	5.000	-1.000	6.000	-1.000
	Q3	8.000	0.000	8.000	0.000
	Max	10.00	1.00	10.00	4.00
Cycle 3	n	69	69	74	74
	Mean	5.014	-1.536	5.284	-1.054
	SD	2.8206	1.9522	3.1077	1.7587
	Min	0.00	-8.00	0.00	-8.00
	Q1	3.000	-2.000	3.000	-2.000
	Median	5.000	-1.000	5.000	-1.000
	Q3	7.000	0.000	8.000	0.000
	Max	10.00	2.00	10.00	2.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 4	n	66	66	73	73
	Mean	4.712	-1.970	4.904	-1.384
	SD	2.8757	1.9293	3.0146	2.2275
	Min	0.00	-8.00	0.00	-9.00
	Q1	3.000	-3.000	3.000	-2.000
	Median	4.500	-2.000	5.000	-1.000
	Q3	7.000	0.000	7.000	0.000
	Max	10.00	2.00	10.00	4.00
Cycle 5	n	65	65	71	71
	Mean	4.600	-2.108	4.944	-1.268
	SD	2.7996	2.4246	3.1977	2.0837
	Min	0.00	-9.00	0.00	-8.00
	Q1	3.000	-3.000	3.000	-2.000
	Median	4.000	-2.000	5.000	-1.000
	Q3	7.000	0.000	7.000	0.000
	Max	10.00	4.00	10.00	3.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 6	n	65	65	70	70
	Mean	4.600	-2.108	4.886	-1.314
	SD	2.9251	2.2369	3.0906	2.1905
	Min	0.00	-9.00	0.00	-9.00
	Q1	3.000	-3.000	3.000	-2.000
	Median	4.000	-2.000	5.000	-1.000
	Q3	7.000	0.000	7.000	0.000
	Max	10.00	3.00	10.00	3.00
Cycle 7	n	65	65	70	70
	Mean	4.400	-2.308	4.629	-1.571
	SD	2.8712	2.2003	3.1585	2.2235
	Min	0.00	-9.00	0.00	-9.00
	Q1	3.000	-4.000	2.000	-3.000
	Median	4.000	-2.000	5.000	-1.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	2.00	10.00	3.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 8	n	65	65	70	70
	Mean	4.415	-2.292	4.729	-1.471
	SD	2.9575	2.0670	3.1250	2.2760
	Min	0.00	-8.00	0.00	-9.00
	Q1	3.000	-4.000	2.000	-3.000
	Median	4.000	-2.000	5.000	-1.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	2.00	10.00	3.00
Cycle 9	n	64	64	69	69
	Mean	4.297	-2.391	4.681	-1.493
	SD	3.0378	2.4078	3.1923	2.3802
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	2.000	-3.000
	Median	4.000	-2.000	5.000	-1.000
	Q3	7.000	-1.000	7.000	0.000
	Max	10.00	2.00	10.00	3.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 10	n	63	63	69	69
	Mean	4.349	-2.302	4.797	-1.377
	SD	2.8064	2.1071	3.2339	2.3646
	Min	0.00	-8.00	0.00	-9.00
	Q1	3.000	-4.000	2.000	-3.000
	Median	4.000	-2.000	5.000	-1.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	1.00	10.00	3.00
Cycle 11	n	62	62	67	67
	Mean	4.258	-2.371	4.493	-1.612
	SD	2.8569	2.1821	3.2021	2.5463
	Min	0.00	-9.00	0.00	-9.00
	Q1	3.000	-3.000	2.000	-3.000
	Median	4.000	-2.000	4.000	-1.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	1.00	10.00	3.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 12	n	62	62	67	67
	Mean	3.903	-2.726	4.642	-1.463
	SD	2.9237	2.2844	3.3015	2.5126
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-4.000	2.000	-3.000
	Median	4.000	-3.000	5.000	-1.000
	Q3	5.000	-1.000	7.000	0.000
	Max	10.00	1.00	10.00	3.00
Cycle 13	n	59	59	64	64
	Mean	4.017	-2.678	4.781	-1.313
	SD	2.9331	2.4666	3.2634	3.1717
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	2.500	-3.000
	Median	4.000	-3.000	4.500	-1.000
	Q3	6.000	-1.000	8.000	0.000
	Max	10.00	2.00	10.00	7.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 14	n	59	59	63	63
	Mean	4.136	-2.559	4.302	-1.762
	SD	2.8735	2.1677	3.1553	2.6984
	Min	0.00	-8.00	0.00	-9.00
	Q1	2.000	-4.000	2.000	-3.000
	Median	4.000	-2.000	4.000	-1.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	1.00	10.00	5.00
Cycle 15	n	58	58	62	62
	Mean	4.207	-2.500	4.081	-2.081
	SD	2.8944	2.3189	3.1378	2.6258
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	1.000	-4.000
	Median	4.000	-2.500	4.000	-2.000
	Q3	7.000	-1.000	6.000	0.000
	Max	10.00	2.00	10.00	3.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 16	n	57	57	62	62
	Mean	3.965	-2.719	4.194	-1.968
	SD	2.8968	2.3280	3.1666	2.6548
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	2.000	-3.000
	Median	4.000	-2.000	4.000	-1.500
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	1.00	10.00	3.00
Cycle 17	n	54	54	61	61
	Mean	3.944	-2.759	4.098	-2.049
	SD	2.8178	2.4720	3.1765	2.4727
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	2.000	-4.000
	Median	3.000	-3.000	4.000	-1.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	2.00	10.00	3.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 18	n	54	54	60	60
	Mean	3.926	-2.778	4.033	-2.083
	SD	2.9258	2.5378	3.0696	2.6122
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	1.000	-3.000
	Median	3.000	-3.000	4.000	-2.000
	Q3	6.000	-1.000	7.000	0.000
	Max	10.00	3.00	10.00	3.00
Cycle 19	n	53	53	59	59
	Mean	4.019	-2.660	3.508	-2.627
	SD	3.0413	2.4490	3.1589	2.9178
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-4.000	0.000	-5.000
	Median	4.000	-3.000	3.000	-2.000
	Q3	6.000	-1.000	6.000	0.000
	Max	10.00	2.00	10.00	3.00

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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 20	n	52	52	58	58
	Mean	3.885	-2.731	3.517	-2.621
	SD	2.8742	2.5904	3.1469	2.8705
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	0.000	-5.000
	Median	4.000	-3.000	3.000	-2.000
	Q3	6.000	-1.000	6.000	0.000
	Max	10.00	4.00	10.00	3.00
Cycle 21	n	50	50	56	56
	Mean	3.900	-2.620	3.750	-2.357
	SD	2.9155	2.4569	3.1923	2.7131
	Min	0.00	-9.00	0.00	-9.00
	Q1	2.000	-4.000	0.500	-4.000
	Median	3.500	-3.000	3.000	-1.000
	Q3	6.000	0.000	6.000	0.000
	Max	10.00	3.00	10.00	3.00

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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 22	n	50	50	56	56
	Mean	3.880	-2.640	3.643	-2.464
	SD	2.9460	2.5214	3.1762	2.8410
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-5.000	1.000	-4.000
	Median	3.500	-2.500	3.000	-2.000
	Q3	6.000	0.000	6.000	0.000
	Max	10.00	3.00	10.00	3.00
Cycle 23	n	51	51	56	56
	Mean	3.843	-2.667	3.500	-2.607
	SD	2.8801	2.6957	3.1795	2.9399
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-4.000	0.500	-5.000
	Median	4.000	-3.000	3.000	-2.000
	Q3	6.000	-1.000	6.000	0.000
	Max	10.00	3.00	10.00	3.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 24	n	50	50	55	55
	Mean	3.780	-2.740	3.036	-3.018
	SD	3.0189	2.7539	3.0910	3.0092
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-4.000	0.000	-5.000
	Median	4.000	-3.000	2.000	-2.000
	Q3	6.000	-1.000	4.000	-1.000
	Max	10.00	4.00	10.00	3.00
Cycle 25	n	47	47	52	52
	Mean	3.574	-2.915	3.058	-3.135
	SD	2.7877	2.6029	3.0896	3.0552
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-4.000	0.000	-5.500
	Median	3.000	-3.000	3.000	-3.000
	Q3	6.000	-1.000	5.000	-0.500
	Max	10.00	2.00	10.00	3.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 26	n	44	44	44	44
	Mean	3.659	-2.682	3.000	-3.341
	SD	2.8032	2.7851	2.8530	2.9250
	Min	0.00	-10.00	0.00	-9.00
	Q1	1.000	-5.000	0.000	-6.000
	Median	3.000	-2.500	2.500	-2.500
	Q3	5.000	0.000	4.500	-1.000
	Max	10.00	3.00	10.00	1.00
Cycle 27	n	37	37	42	42
	Mean	3.595	-2.892	3.119	-3.238
	SD	3.0319	2.8847	2.9067	3.2745
	Min	0.00	-10.00	0.00	-9.00
	Q1	1.000	-4.000	1.000	-6.000
	Median	3.000	-3.000	2.500	-2.000
	Q3	6.000	-1.000	4.000	0.000
	Max	10.00	2.00	10.00	2.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 28	n	34	34	37	37
	Mean	3.441	-2.618	3.135	-3.027
	SD	3.0371	2.8921	3.1373	3.2531
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-5.000	0.000	-6.000
	Median	3.000	-3.000	3.000	-2.000
	Q3	5.000	0.000	4.000	0.000
	Max	10.00	3.00	10.00	2.00
Cycle 29	n	30	30	35	35
	Mean	3.233	-2.700	2.543	-3.143
	SD	2.8246	2.5617	2.5821	2.8712
	Min	0.00	-9.00	0.00	-9.00
	Q1	1.000	-4.000	0.000	-5.000
	Median	3.000	-2.000	2.000	-2.000
	Q3	5.000	-1.000	4.000	-1.000
	Max	10.00	1.00	8.00	1.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 30	n	28	28	30	30
	Mean	3.357	-2.464	2.167	-3.400
	SD	2.9214	2.7282	2.6403	3.1797
	Min	0.00	-10.00	0.00	-9.00
	Q1	0.500	-4.000	0.000	-6.000
	Median	3.000	-1.500	1.000	-2.000
	Q3	5.000	0.000	4.000	-1.000
	Max	10.00	1.00	8.00	1.00
Cycle 31	n	23	23	25	25
	Mean	2.957	-2.522	2.600	-2.480
	SD	3.0072	2.7940	3.0822	2.6789
	Min	0.00	-10.00	0.00	-8.00
	Q1	0.000	-4.000	0.000	-5.000
	Median	3.000	-2.000	2.000	-2.000
	Q3	5.000	-1.000	4.000	0.000
	Max	10.00	2.00	10.00	2.00

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Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 32	n	17	17	21	21
	Mean	4.059	-2.176	2.524	-2.810
	SD	3.0305	1.8109	2.9769	2.9261
	Min	0.00	-5.00	0.00	-8.00
	Q1	1.000	-3.000	0.000	-6.000
	Median	4.000	-3.000	2.000	-2.000
	Q3	6.000	-2.000	3.000	-1.000
	Max	10.00	2.00	10.00	3.00
Cycle 33	n	12	12	16	16
	Mean	3.667	-2.917	2.375	-2.813
	SD	2.9336	1.5050	2.8018	2.7379
	Min	0.00	-4.00	0.00	-7.00
	Q1	1.500	-4.000	0.000	-5.000
	Median	3.500	-3.500	1.500	-2.000
	Q3	5.500	-2.500	4.000	-1.000
	Max	10.00	0.00	8.00	1.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 34	n	8	8	10	10
	Mean	4.000	-3.875	3.300	-2.800
	SD	3.8545	3.2266	3.0203	2.7406
	Min	0.00	-10.00	0.00	-7.00
	Q1	0.000	-5.500	0.000	-5.000
	Median	4.000	-3.000	3.000	-2.500
	Q3	7.000	-2.000	5.000	-1.000
	Max	10.00	0.00	8.00	1.00
Cycle 35	n	8	8	9	9
	Mean	4.125	-3.750	4.000	-2.111
	SD	3.3139	2.8158	3.1623	2.5712
	Min	0.00	-10.00	0.00	-7.00
	Q1	1.500	-4.000	3.000	-4.000
	Median	4.000	-3.000	3.000	-1.000
	Q3	6.000	-3.000	6.000	0.000
	Max	10.00	0.00	9.00	1.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 36	n	6	6	9	9
	Mean	4.333	-3.333	3.889	-2.222
	SD	4.1312	2.5820	2.9768	2.4889
	Min	0.00	-7.00	0.00	-7.00
	Q1	0.000	-5.000	3.000	-4.000
	Median	4.000	-3.500	3.000	-1.000
	Q3	8.000	-1.000	6.000	-1.000
	Max	10.00	0.00	8.00	1.00
Cycle 37	n	6	6	9	9
	Mean	4.500	-3.167	4.444	-1.667
	SD	3.5637	1.7224	3.2447	2.3979
	Min	0.00	-5.00	0.00	-7.00
	Q1	2.000	-4.000	3.000	-2.000
	Median	4.500	-3.500	4.000	-1.000
	Q3	6.000	-3.000	7.000	0.000
	Max	10.00	0.00	9.00	0.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 38	n	6	6	9	9
	Mean	4.500	-3.167	4.000	-2.111
	SD	3.3912	1.7224	3.1623	2.5712
	Min	0.00	-5.00	0.00	-7.00
	Q1	3.000	-4.000	3.000	-4.000
	Median	4.000	-3.500	3.000	-1.000
	Q3	6.000	-3.000	6.000	0.000
	Max	10.00	0.00	9.00	1.00
Cycle 39	n	5	5	7	7
	Mean	4.800	-3.000	4.000	-1.857
	SD	3.7014	1.7321	3.3665	2.6726
	Min	0.00	-4.00	0.00	-7.00
	Q1	3.000	-4.000	0.000	-4.000
	Median	5.000	-4.000	4.000	-1.000
	Q3	6.000	-3.000	7.000	0.000
	Max	10.00	0.00	9.00	0.00

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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 40	n	3	3	7	7
	Mean	6.667	-3.000	4.143	-1.714
	SD	3.0551	2.6458	3.3381	2.4300
	Min	4.00	-5.00	0.00	-7.00
	Q1	4.000	-5.000	0.000	-2.000
	Median	6.000	-4.000	4.000	-1.000
	Q3	10.000	0.000	7.000	0.000
	Max	10.00	0.00	8.00	0.00
Cycle 41	n	2	2	3	3
	Mean	8.000	-2.000	3.000	-3.667
	SD	2.8284	2.8284	3.0000	3.0551
	Min	6.00	-4.00	0.00	-7.00
	Q1	6.000	-4.000	0.000	-7.000
	Median	8.000	-2.000	3.000	-3.000
	Q3	10.000	0.000	6.000	-1.000
	Max	10.00	0.00	6.00	-1.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.17.1 PAINS-pNF spike target PN pain intensity scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 42	n	2	2	2	2
	Mean	7.500	-2.500	1.500	-4.000
	SD	3.5355	3.5355	2.1213	4.2426
	Min	5.00	-5.00	0.00	-7.00
	Q1	5.000	-5.000	0.000	-7.000
	Median	7.500	-2.500	1.500	-4.000
	Q3	10.000	0.000	3.000	-1.000
	Max	10.00	0.00	3.00	-1.00

Baseline score is the maximum score over the screening period. Post-baseline score is the maximum score in 28-day cycle. A higher PAINS-pNF spike target PN pain intensity score is worse. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group.
PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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1.3.3 Schmerz anhand PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch – Veränderung zu Baseline

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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 1	Total non-missing	n	71	70
	Increased	n (%)	2 (2.8)	4 (5.7)
	Increased >=1 point	n (%)	0	0
	Increased 0.5 point	n (%)	2 (2.8)	4 (5.7)
	No change	n (%)	57 (80.3)	62 (88.6)
	Decreased	n (%)	12 (16.9)	4 (5.7)
Cycle 2	Total non-missing	n	68	70
	Increased	n (%)	2 (2.9)	7 (10.0)
	Increased >=1 point	n (%)	0	1 (1.4)
	Increased 0.5 point	n (%)	2 (2.9)	6 (8.6)
	No change	n (%)	56 (82.4)	60 (85.7)
	Decreased	n (%)	10 (14.7)	3 (4.3)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 3	Total non-missing	n	67	70
	Increased	n (%)	3 (4.5)	7 (10.0)
	Increased >=1 point	n (%)	1 (1.5)	1 (1.4)
	Increased 0.5 point	n (%)	2 (3.0)	6 (8.6)
	No change	n (%)	46 (68.7)	55 (78.6)
	Decreased	n (%)	18 (26.9)	8 (11.4)
Cycle 4	Total non-missing	n	65	70
	Increased	n (%)	1 (1.5)	5 (7.1)
	Increased >=1 point	n (%)	0	1 (1.4)
	Increased 0.5 point	n (%)	1 (1.5)	4 (5.7)
	No change	n (%)	48 (73.8)	56 (80.0)
	Decreased	n (%)	16 (24.6)	9 (12.9)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 5	Total non-missing	n	65	67
	Increased	n (%)	1 (1.5)	4 (6.0)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	1 (1.5)	3 (4.5)
	No change	n (%)	44 (67.7)	54 (80.6)
	Decreased	n (%)	20 (30.8)	9 (13.4)
Cycle 6	Total non-missing	n	65	67
	Increased	n (%)	1 (1.5)	6 (9.0)
	Increased >=1 point	n (%)	0	2 (3.0)
	Increased 0.5 point	n (%)	1 (1.5)	4 (6.0)
	No change	n (%)	47 (72.3)	56 (83.6)
	Decreased	n (%)	17 (26.2)	5 (7.5)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 7	Total non-missing	n	65	67
	Increased	n (%)	0	7 (10.4)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	0	6 (9.0)
	No change	n (%)	48 (73.8)	52 (77.6)
	Decreased	n (%)	17 (26.2)	8 (11.9)
Cycle 8	Total non-missing	n	64	67
	Increased	n (%)	2 (3.1)	8 (11.9)
	Increased >=1 point	n (%)	1 (1.6)	2 (3.0)
	Increased 0.5 point	n (%)	1 (1.6)	6 (9.0)
	No change	n (%)	48 (75.0)	53 (79.1)
	Decreased	n (%)	14 (21.9)	6 (9.0)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 9	Total non-missing	n	62	65
	Increased	n (%)	1 (1.6)	6 (9.2)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	1 (1.6)	5 (7.7)
	No change	n (%)	44 (71.0)	51 (78.5)
	Decreased	n (%)	17 (27.4)	8 (12.3)
Cycle 10	Total non-missing	n	61	65
	Increased	n (%)	1 (1.6)	7 (10.8)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	1 (1.6)	6 (9.2)
	No change	n (%)	42 (68.9)	49 (75.4)
	Decreased	n (%)	18 (29.5)	9 (13.8)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 11	Total non-missing	n	59	66
	Increased	n (%)	2 (3.4)	6 (9.1)
	Increased >=1 point	n (%)	0	1 (1.5)
	Increased 0.5 point	n (%)	2 (3.4)	5 (7.6)
	No change	n (%)	40 (67.8)	51 (77.3)
	Decreased	n (%)	17 (28.8)	9 (13.6)
Cycle 12	Total non-missing	n	59	63
	Increased	n (%)	2 (3.4)	5 (7.9)
	Increased >=1 point	n (%)	0	1 (1.6)
	Increased 0.5 point	n (%)	2 (3.4)	4 (6.3)
	No change	n (%)	41 (69.5)	49 (77.8)
	Decreased	n (%)	16 (27.1)	9 (14.3)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 13	Total non-missing	n	58	61
	Increased	n (%)	2 (3.4)	5 (8.2)
	Increased >=1 point	n (%)	0	2 (3.3)
	Increased 0.5 point	n (%)	2 (3.4)	3 (4.9)
	No change	n (%)	40 (69.0)	47 (77.0)
	Decreased	n (%)	16 (27.6)	9 (14.8)
Cycle 14	Total non-missing	n	59	60
	Increased	n (%)	2 (3.4)	4 (6.7)
	Increased >=1 point	n (%)	1 (1.7)	2 (3.3)
	Increased 0.5 point	n (%)	1 (1.7)	2 (3.3)
	No change	n (%)	41 (69.5)	44 (73.3)
	Decreased	n (%)	16 (27.1)	12 (20.0)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 15	Total non-missing	n	57	59
	Increased	n (%)	1 (1.8)	5 (8.5)
	Increased >=1 point	n (%)	0	2 (3.4)
	Increased 0.5 point	n (%)	1 (1.8)	3 (5.1)
	No change	n (%)	39 (68.4)	43 (72.9)
	Decreased	n (%)	17 (29.8)	11 (18.6)
Cycle 16	Total non-missing	n	56	59
	Increased	n (%)	1 (1.8)	4 (6.8)
	Increased >=1 point	n (%)	0	2 (3.4)
	Increased 0.5 point	n (%)	1 (1.8)	2 (3.4)
	No change	n (%)	38 (67.9)	44 (74.6)
	Decreased	n (%)	17 (30.4)	11 (18.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 17	Total non-missing	n	54	59
	Increased	n (%)	2 (3.7)	5 (8.5)
	Increased >=1 point	n (%)	0	3 (5.1)
	Increased 0.5 point	n (%)	2 (3.7)	2 (3.4)
	No change	n (%)	37 (68.5)	43 (72.9)
	Decreased	n (%)	15 (27.8)	11 (18.6)
Cycle 18	Total non-missing	n	54	56
	Increased	n (%)	2 (3.7)	4 (7.1)
	Increased >=1 point	n (%)	0	2 (3.6)
	Increased 0.5 point	n (%)	2 (3.7)	2 (3.6)
	No change	n (%)	35 (64.8)	41 (73.2)
	Decreased	n (%)	17 (31.5)	11 (19.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 19	Total non-missing	n	53	56
	Increased	n (%)	1 (1.9)	3 (5.4)
	Increased >=1 point	n (%)	0	2 (3.6)
	Increased 0.5 point	n (%)	1 (1.9)	1 (1.8)
	No change	n (%)	36 (67.9)	42 (75.0)
	Decreased	n (%)	16 (30.2)	11 (19.6)
Cycle 20	Total non-missing	n	51	56
	Increased	n (%)	0	5 (8.9)
	Increased >=1 point	n (%)	0	2 (3.6)
	Increased 0.5 point	n (%)	0	3 (5.4)
	No change	n (%)	35 (68.6)	38 (67.9)
	Decreased	n (%)	16 (31.4)	13 (23.2)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 21	Total non-missing	n	50	53
	Increased	n (%)	0	5 (9.4)
	Increased >=1 point	n (%)	0	2 (3.8)
	Increased 0.5 point	n (%)	0	3 (5.7)
	No change	n (%)	31 (62.0)	36 (67.9)
	Decreased	n (%)	19 (38.0)	12 (22.6)
Cycle 22	Total non-missing	n	50	53
	Increased	n (%)	1 (2.0)	3 (5.7)
	Increased >=1 point	n (%)	1 (2.0)	2 (3.8)
	Increased 0.5 point	n (%)	0	1 (1.9)
	No change	n (%)	34 (68.0)	38 (71.7)
	Decreased	n (%)	15 (30.0)	12 (22.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 23	Total non-missing	n	50	54
	Increased	n (%)	1 (2.0)	5 (9.3)
	Increased >=1 point	n (%)	1 (2.0)	3 (5.6)
	Increased 0.5 point	n (%)	0	2 (3.7)
	No change	n (%)	31 (62.0)	37 (68.5)
	Decreased	n (%)	18 (36.0)	12 (22.2)
Cycle 24	Total non-missing	n	50	53
	Increased	n (%)	0	3 (5.7)
	Increased >=1 point	n (%)	0	0
	Increased 0.5 point	n (%)	0	3 (5.7)
	No change	n (%)	33 (66.0)	38 (71.7)
	Decreased	n (%)	17 (34.0)	12 (22.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 25	Total non-missing	n	47	51
	Increased	n (%)	0	2 (3.9)
	Increased >=1 point	n (%)	0	1 (2.0)
	Increased 0.5 point	n (%)	0	1 (2.0)
	No change	n (%)	30 (63.8)	34 (66.7)
	Decreased	n (%)	17 (36.2)	15 (29.4)
Cycle 26	Total non-missing	n	42	43
	Increased	n (%)	0	2 (4.7)
	Increased >=1 point	n (%)	0	1 (2.3)
	Increased 0.5 point	n (%)	0	1 (2.3)
	No change	n (%)	27 (64.3)	29 (67.4)
	Decreased	n (%)	15 (35.7)	12 (27.9)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 27	Total non-missing	n	37	41
	Increased	n (%)	0	2 (4.9)
	Increased >=1 point	n (%)	0	1 (2.4)
	Increased 0.5 point	n (%)	0	1 (2.4)
	No change	n (%)	23 (62.2)	28 (68.3)
	Decreased	n (%)	14 (37.8)	11 (26.8)
Cycle 28	Total non-missing	n	34	35
	Increased	n (%)	0	2 (5.7)
	Increased >=1 point	n (%)	0	1 (2.9)
	Increased 0.5 point	n (%)	0	1 (2.9)
	No change	n (%)	22 (64.7)	24 (68.6)
	Decreased	n (%)	12 (35.3)	9 (25.7)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 29	Total non-missing	n	30	34
	Increased	n (%)	0	2 (5.9)
	Increased >=1 point	n (%)	0	1 (2.9)
	Increased 0.5 point	n (%)	0	1 (2.9)
	No change	n (%)	21 (70.0)	25 (73.5)
	Decreased	n (%)	9 (30.0)	7 (20.6)
Cycle 30	Total non-missing	n	28	29
	Increased	n (%)	0	1 (3.4)
	Increased >=1 point	n (%)	0	1 (3.4)
	Increased 0.5 point	n (%)	0	0
	No change	n (%)	19 (67.9)	21 (72.4)
	Decreased	n (%)	9 (32.1)	7 (24.1)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 31	Total non-missing	n	23	25
	Increased	n (%)	1 (4.3)	2 (8.0)
	Increased >=1 point	n (%)	0	1 (4.0)
	Increased 0.5 point	n (%)	1 (4.3)	1 (4.0)
	No change	n (%)	16 (69.6)	20 (80.0)
	Decreased	n (%)	6 (26.1)	3 (12.0)
Cycle 32	Total non-missing	n	17	21
	Increased	n (%)	0	2 (9.5)
	Increased >=1 point	n (%)	0	1 (4.8)
	Increased 0.5 point	n (%)	0	1 (4.8)
	No change	n (%)	11 (64.7)	17 (81.0)
	Decreased	n (%)	6 (35.3)	2 (9.5)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 33	Total non-missing	n	12	16
	Increased	n (%)	0	2 (12.5)
	Increased >=1 point	n (%)	0	1 (6.3)
	Increased 0.5 point	n (%)	0	1 (6.3)
	No change	n (%)	9 (75.0)	13 (81.3)
	Decreased	n (%)	3 (25.0)	1 (6.3)
Cycle 34	Total non-missing	n	7	10
	Increased	n (%)	0	2 (20.0)
	Increased >=1 point	n (%)	0	1 (10.0)
	Increased 0.5 point	n (%)	0	1 (10.0)
	No change	n (%)	4 (57.1)	8 (80.0)
	Decreased	n (%)	3 (42.9)	0

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 35	Total non-missing	n	8	9
	Increased	n (%)	0	1 (11.1)
	Increased >=1 point	n (%)	0	1 (11.1)
	Increased 0.5 point	n (%)	0	0
	No change	n (%)	5 (62.5)	7 (77.8)
	Decreased	n (%)	3 (37.5)	1 (11.1)
Cycle 36	Total non-missing	n	6	9
	Increased	n (%)	0	2 (22.2)
	Increased >=1 point	n (%)	0	1 (11.1)
	Increased 0.5 point	n (%)	0	1 (11.1)
	No change	n (%)	5 (83.3)	7 (77.8)
	Decreased	n (%)	1 (16.7)	0

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Final DCO PSC
Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 37	Total non-missing	n	6	9
	Increased	n (%)	0	2 (22.2)
	Increased >=1 point	n (%)	0	1 (11.1)
	Increased 0.5 point	n (%)	0	1 (11.1)
	No change	n (%)	4 (66.7)	6 (66.7)
	Decreased	n (%)	2 (33.3)	1 (11.1)
Cycle 38	Total non-missing	n	6	9
	Increased	n (%)	0	2 (22.2)
	Increased >=1 point	n (%)	0	1 (11.1)
	Increased 0.5 point	n (%)	0	1 (11.1)
	No change	n (%)	5 (83.3)	6 (66.7)
	Decreased	n (%)	1 (16.7)	1 (11.1)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 39	Total non-missing	n	5	7
	Increased	n (%)	0	1 (14.3)
	Increased >=1 point	n (%)	0	1 (14.3)
	Increased 0.5 point	n (%)	0	0
	No change	n (%)	4 (80.0)	5 (71.4)
	Decreased	n (%)	1 (20.0)	1 (14.3)
Cycle 40	Total non-missing	n	3	7
	Increased	n (%)	0	1 (14.3)
	Increased >=1 point	n (%)	0	1 (14.3)
	Increased 0.5 point	n (%)	0	0
	No change	n (%)	2 (66.7)	5 (71.4)
	Decreased	n (%)	1 (33.3)	1 (14.3)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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Table 14.2.11.1.3 Change from baseline in chronic PN pain medication (Full analysis set)

Timepoint	Category	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 41	Total non-missing	n	2	3
	Increased	n (%)	0	0
	Increased >=1 point	n (%)	0	0
	Increased 0.5 point	n (%)	0	0
	No change	n (%)	2 (100)	3 (100)
	Decreased	n (%)	0	0
Cycle 42	Total non-missing	n	2	2
	Increased	n (%)	0	0
	Increased >=1 point	n (%)	0	0
	Increased 0.5 point	n (%)	0	0
	No change	n (%)	2 (100)	2 (100)
	Decreased	n (%)	0	0

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (score range = 1 (lowest) - 4 (highest)) (see statistical analysis plan). Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). An increase from baseline occurs if a specific drug has a higher analgesic ladder score than baseline (increase of >=1). Or, if a specific drug has the same analgesic ladder score as baseline which is >=2; if there is an increase in max daily dose or number of medications of this class compared to baseline (increase of >=0.5). Specific drug must be in the highest class taken for >=3 days in a cycle and increase in dose or number of medications must be for >=3 days in cycle to meet requirement for increase. n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO World Health Organization. Full analysis set - subjectsrandomised to study intervention.
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1.3.4 Schmerz anhand PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch – Werte im Studienverlauf

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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Baseline	Total non-missing	n	71	72
	0-No Analgesia	n (%)	33 (46.5)	37 (51.4)
	1-Non-opioids	n (%)	15 (21.1)	11 (15.3)
	2-Neuropathic/other non-typical pain medications	n (%)	18 (25.4)	12 (16.7)
	3-Weak opioids	n (%)	2 (2.8)	3 (4.2)
	4-Strong opioids	n (%)	3 (4.2)	9 (12.5)
Cycle 1	Total non-missing	n	71	70
	0-No Analgesia	n (%)	43 (60.6)	40 (57.1)
	1-Non-opioids	n (%)	11 (15.5)	7 (10.0)
	2-Neuropathic/other non-typical pain medications	n (%)	12 (16.9)	11 (15.7)
	3-Weak opioids	n (%)	2 (2.8)	3 (4.3)
	4-Strong opioids	n (%)	3 (4.2)	9 (12.9)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 2	Total non-missing	n	68	70
	0-No Analgesia	n (%)	42 (61.8)	36 (51.4)
	1-Non-opioids	n (%)	9 (13.2)	10 (14.3)
	2-Neuropathic/other non-typical pain medications	n (%)	12 (17.6)	10 (14.3)
	3-Weak opioids	n (%)	2 (2.9)	4 (5.7)
	4-Strong opioids	n (%)	3 (4.4)	10 (14.3)
Cycle 3	Total non-missing	n	67	70
	0-No Analgesia	n (%)	46 (68.7)	42 (60.0)
	1-Non-opioids	n (%)	6 (9.0)	6 (8.6)
	2-Neuropathic/other non-typical pain medications	n (%)	11 (16.4)	10 (14.3)
	3-Weak opioids	n (%)	2 (3.0)	2 (2.9)
	4-Strong opioids	n (%)	2 (3.0)	10 (14.3)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 4	Total non-missing	n	65	70
	0-No Analgesia	n (%)	44 (67.7)	42 (60.0)
	1-Non-opioids	n (%)	6 (9.2)	6 (8.6)
	2-Neuropathic/other non-typical pain medications	n (%)	11 (16.9)	11 (15.7)
	3-Weak opioids	n (%)	2 (3.1)	2 (2.9)
	4-Strong opioids	n (%)	2 (3.1)	9 (12.9)
Cycle 5	Total non-missing	n	65	67
	0-No Analgesia	n (%)	49 (75.4)	42 (62.7)
	1-Non-opioids	n (%)	5 (7.7)	6 (9.0)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (12.3)	8 (11.9)
	3-Weak opioids	n (%)	2 (3.1)	3 (4.5)
	4-Strong opioids	n (%)	1 (1.5)	8 (11.9)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 6	Total non-missing	n	65	67
	0-No Analgesia	n (%)	45 (69.2)	38 (56.7)
	1-Non-opioids	n (%)	5 (7.7)	7 (10.4)
	2-Neuropathic/other non-typical pain medications	n (%)	11 (16.9)	10 (14.9)
	3-Weak opioids	n (%)	2 (3.1)	4 (6.0)
	4-Strong opioids	n (%)	2 (3.1)	8 (11.9)
Cycle 7	Total non-missing	n	65	67
	0-No Analgesia	n (%)	44 (67.7)	41 (61.2)
	1-Non-opioids	n (%)	7 (10.8)	5 (7.5)
	2-Neuropathic/other non-typical pain medications	n (%)	9 (13.8)	10 (14.9)
	3-Weak opioids	n (%)	3 (4.6)	4 (6.0)
	4-Strong opioids	n (%)	2 (3.1)	7 (10.4)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 8	Total non-missing	n	64	67
	0-No Analgesia	n (%)	40 (62.5)	39 (58.2)
	1-Non-opioids	n (%)	5 (7.8)	7 (10.4)
	2-Neuropathic/other non-typical pain medications	n (%)	12 (18.8)	11 (16.4)
	3-Weak opioids	n (%)	5 (7.8)	2 (3.0)
	4-Strong opioids	n (%)	2 (3.1)	8 (11.9)
Cycle 9	Total non-missing	n	62	65
	0-No Analgesia	n (%)	41 (66.1)	42 (64.6)
	1-Non-opioids	n (%)	6 (9.7)	5 (7.7)
	2-Neuropathic/other non-typical pain medications	n (%)	10 (16.1)	9 (13.8)
	3-Weak opioids	n (%)	3 (4.8)	2 (3.1)
	4-Strong opioids	n (%)	2 (3.2)	7 (10.8)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 10	Total non-missing	n	61	65
	0-No Analgesia	n (%)	44 (72.1)	41 (63.1)
	1-Non-opioids	n (%)	6 (9.8)	4 (6.2)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (13.1)	10 (15.4)
	3-Weak opioids	n (%)	1 (1.6)	2 (3.1)
	4-Strong opioids	n (%)	2 (3.3)	8 (12.3)
Cycle 11	Total non-missing	n	59	66
	0-No Analgesia	n (%)	43 (72.9)	41 (62.1)
	1-Non-opioids	n (%)	5 (8.5)	6 (9.1)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (13.6)	9 (13.6)
	3-Weak opioids	n (%)	1 (1.7)	3 (4.5)
	4-Strong opioids	n (%)	2 (3.4)	7 (10.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 12	Total non-missing	n	59	63
	0-No Analgesia	n (%)	41 (69.5)	41 (65.1)
	1-Non-opioids	n (%)	7 (11.9)	4 (6.3)
	2-Neuropathic/other non-typical pain medications	n (%)	9 (15.3)	7 (11.1)
	3-Weak opioids	n (%)	0	3 (4.8)
	4-Strong opioids	n (%)	2 (3.4)	8 (12.7)
Cycle 13	Total non-missing	n	58	61
	0-No Analgesia	n (%)	38 (65.5)	39 (63.9)
	1-Non-opioids	n (%)	8 (13.8)	5 (8.2)
	2-Neuropathic/other non-typical pain medications	n (%)	9 (15.5)	6 (9.8)
	3-Weak opioids	n (%)	0	2 (3.3)
	4-Strong opioids	n (%)	3 (5.2)	9 (14.8)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 14	Total non-missing	n	59	60
	0-No Analgesia	n (%)	40 (67.8)	40 (66.7)
	1-Non-opioids	n (%)	7 (11.9)	5 (8.3)
	2-Neuropathic/other non-typical pain medications	n (%)	8 (13.6)	5 (8.3)
	3-Weak opioids	n (%)	1 (1.7)	3 (5.0)
	4-Strong opioids	n (%)	3 (5.1)	7 (11.7)
Cycle 15	Total non-missing	n	57	59
	0-No Analgesia	n (%)	42 (73.7)	42 (71.2)
	1-Non-opioids	n (%)	5 (8.8)	2 (3.4)
	2-Neuropathic/other non-typical pain medications	n (%)	7 (12.3)	6 (10.2)
	3-Weak opioids	n (%)	1 (1.8)	1 (1.7)
	4-Strong opioids	n (%)	2 (3.5)	8 (13.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 16	Total non-missing	n	56	59
	0-No Analgesia	n (%)	41 (73.2)	40 (67.8)
	1-Non-opioids	n (%)	7 (12.5)	2 (3.4)
	2-Neuropathic/other non-typical pain medications	n (%)	5 (8.9)	7 (11.9)
	3-Weak opioids	n (%)	1 (1.8)	2 (3.4)
	4-Strong opioids	n (%)	2 (3.6)	8 (13.6)
Cycle 17	Total non-missing	n	54	59
	0-No Analgesia	n (%)	39 (72.2)	39 (66.1)
	1-Non-opioids	n (%)	8 (14.8)	4 (6.8)
	2-Neuropathic/other non-typical pain medications	n (%)	5 (9.3)	7 (11.9)
	3-Weak opioids	n (%)	1 (1.9)	1 (1.7)
	4-Strong opioids	n (%)	1 (1.9)	8 (13.6)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 18	Total non-missing	n	54	56
	0-No Analgesia	n (%)	41 (75.9)	40 (71.4)
	1-Non-opioids	n (%)	4 (7.4)	1 (1.8)
	2-Neuropathic/other non-typical pain medications	n (%)	5 (9.3)	7 (12.5)
	3-Weak opioids	n (%)	2 (3.7)	1 (1.8)
	4-Strong opioids	n (%)	2 (3.7)	7 (12.5)
Cycle 19	Total non-missing	n	53	56
	0-No Analgesia	n (%)	40 (75.5)	39 (69.6)
	1-Non-opioids	n (%)	5 (9.4)	2 (3.6)
	2-Neuropathic/other non-typical pain medications	n (%)	6 (11.3)	6 (10.7)
	3-Weak opioids	n (%)	0	2 (3.6)
	4-Strong opioids	n (%)	2 (3.8)	7 (12.5)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 20	Total non-missing	n	51	56
	0-No Analgesia	n (%)	37 (72.5)	41 (73.2)
	1-Non-opioids	n (%)	7 (13.7)	1 (1.8)
	2-Neuropathic/other non-typical pain medications	n (%)	5 (9.8)	7 (12.5)
	3-Weak opioids	n (%)	0	1 (1.8)
	4-Strong opioids	n (%)	2 (3.9)	6 (10.7)
Cycle 21	Total non-missing	n	50	53
	0-No Analgesia	n (%)	41 (82.0)	38 (71.7)
	1-Non-opioids	n (%)	3 (6.0)	1 (1.9)
	2-Neuropathic/other non-typical pain medications	n (%)	5 (10.0)	6 (11.3)
	3-Weak opioids	n (%)	0	1 (1.9)
	4-Strong opioids	n (%)	1 (2.0)	7 (13.2)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 22	Total non-missing	n	50	53
	0-No Analgesia	n (%)	38 (76.0)	38 (71.7)
	1-Non-opioids	n (%)	3 (6.0)	1 (1.9)
	2-Neuropathic/other non-typical pain medications	n (%)	6 (12.0)	6 (11.3)
	3-Weak opioids	n (%)	2 (4.0)	1 (1.9)
	4-Strong opioids	n (%)	1 (2.0)	7 (13.2)
Cycle 23	Total non-missing	n	50	54
	0-No Analgesia	n (%)	39 (78.0)	38 (70.4)
	1-Non-opioids	n (%)	3 (6.0)	1 (1.9)
	2-Neuropathic/other non-typical pain medications	n (%)	6 (12.0)	8 (14.8)
	3-Weak opioids	n (%)	1 (2.0)	1 (1.9)
	4-Strong opioids	n (%)	1 (2.0)	6 (11.1)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 24	Total non-missing	n	50	53
	0-No Analgesia	n (%)	38 (76.0)	38 (71.7)
	1-Non-opioids	n (%)	5 (10.0)	1 (1.9)
	2-Neuropathic/other non-typical pain medications	n (%)	6 (12.0)	8 (15.1)
	3-Weak opioids	n (%)	0	1 (1.9)
	4-Strong opioids	n (%)	1 (2.0)	5 (9.4)
Cycle 25	Total non-missing	n	47	51
	0-No Analgesia	n (%)	37 (78.7)	37 (72.5)
	1-Non-opioids	n (%)	3 (6.4)	1 (2.0)
	2-Neuropathic/other non-typical pain medications	n (%)	5 (10.6)	11 (21.6)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	2 (4.3)	2 (3.9)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 26	Total non-missing	n	42	43
	0-No Analgesia	n (%)	32 (76.2)	32 (74.4)
	1-Non-opioids	n (%)	3 (7.1)	1 (2.3)
	2-Neuropathic/other non-typical pain medications	n (%)	6 (14.3)	7 (16.3)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	1 (2.4)	3 (7.0)
Cycle 27	Total non-missing	n	37	41
	0-No Analgesia	n (%)	31 (83.8)	30 (73.2)
	1-Non-opioids	n (%)	1 (2.7)	2 (4.9)
	2-Neuropathic/other non-typical pain medications	n (%)	3 (8.1)	6 (14.6)
	3-Weak opioids	n (%)	1 (2.7)	0
	4-Strong opioids	n (%)	1 (2.7)	3 (7.3)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 28	Total non-missing	n	34	35
	0-No Analgesia	n (%)	27 (79.4)	27 (77.1)
	1-Non-opioids	n (%)	2 (5.9)	2 (5.7)
	2-Neuropathic/other non-typical pain medications	n (%)	3 (8.8)	4 (11.4)
	3-Weak opioids	n (%)	1 (2.9)	0
	4-Strong opioids	n (%)	1 (2.9)	2 (5.7)
Cycle 29	Total non-missing	n	30	34
	0-No Analgesia	n (%)	22 (73.3)	26 (76.5)
	1-Non-opioids	n (%)	2 (6.7)	2 (5.9)
	2-Neuropathic/other non-typical pain medications	n (%)	4 (13.3)	4 (11.8)
	3-Weak opioids	n (%)	1 (3.3)	0
	4-Strong opioids	n (%)	1 (3.3)	2 (5.9)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 30	Total non-missing	n	28	29
	0-No Analgesia	n (%)	22 (78.6)	23 (79.3)
	1-Non-opioids	n (%)	2 (7.1)	1 (3.4)
	2-Neuropathic/other non-typical pain medications	n (%)	2 (7.1)	3 (10.3)
	3-Weak opioids	n (%)	1 (3.6)	0
	4-Strong opioids	n (%)	1 (3.6)	2 (6.9)
Cycle 31	Total non-missing	n	23	25
	0-No Analgesia	n (%)	18 (78.3)	19 (76.0)
	1-Non-opioids	n (%)	2 (8.7)	0
	2-Neuropathic/other non-typical pain medications	n (%)	2 (8.7)	3 (12.0)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	1 (4.3)	3 (12.0)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 32	Total non-missing	n	17	21
	0-No Analgesia	n (%)	13 (76.5)	15 (71.4)
	1-Non-opioids	n (%)	1 (5.9)	1 (4.8)
	2-Neuropathic/other non-typical pain medications	n (%)	2 (11.8)	3 (14.3)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	1 (5.9)	2 (9.5)
Cycle 33	Total non-missing	n	12	16
	0-No Analgesia	n (%)	8 (66.7)	12 (75.0)
	1-Non-opioids	n (%)	1 (8.3)	0
	2-Neuropathic/other non-typical pain medications	n (%)	2 (16.7)	2 (12.5)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	1 (8.3)	2 (12.5)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff249.sas
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Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 34	Total non-missing	n	7	10
	0-No Analgesia	n (%)	5 (71.4)	6 (60.0)
	1-Non-opioids	n (%)	1 (14.3)	1 (10.0)
	2-Neuropathic/other non-typical pain medications	n (%)	1 (14.3)	1 (10.0)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	2 (20.0)
Cycle 35	Total non-missing	n	8	9
	0-No Analgesia	n (%)	6 (75.0)	6 (66.7)
	1-Non-opioids	n (%)	1 (12.5)	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (12.5)	1 (11.1)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	2 (22.2)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 36	Total non-missing	n	6	9
	0-No Analgesia	n (%)	4 (66.7)	5 (55.6)
	1-Non-opioids	n (%)	1 (16.7)	1 (11.1)
	2-Neuropathic/other non-typical pain medications	n (%)	1 (16.7)	1 (11.1)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	2 (22.2)
Cycle 37	Total non-missing	n	6	9
	0-No Analgesia	n (%)	5 (83.3)	6 (66.7)
	1-Non-opioids	n (%)	0	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (16.7)	1 (11.1)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	2 (22.2)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff249.sas
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 38	Total non-missing	n	6	9
	0-No Analgesia	n (%)	4 (66.7)	6 (66.7)
	1-Non-opioids	n (%)	1 (16.7)	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (16.7)	1 (11.1)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	2 (22.2)
Cycle 39	Total non-missing	n	5	7
	0-No Analgesia	n (%)	3 (60.0)	5 (71.4)
	1-Non-opioids	n (%)	1 (20.0)	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (20.0)	1 (14.3)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	1 (14.3)

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff249.sas
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 40	Total non-missing	n	3	7
	0-No Analgesia	n (%)	2 (66.7)	5 (71.4)
	1-Non-opioids	n (%)	0	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (33.3)	1 (14.3)
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	1 (14.3)
Cycle 41	Total non-missing	n	2	3
	0-No Analgesia	n (%)	1 (50.0)	3 (100)
	1-Non-opioids	n (%)	0	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (50.0)	0
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	0

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff249.sas
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Final DCO PSC
Table 14.2.11.1.1 Chronic PN pain medication strongest analgesic ladder class and score by cycle (Full analysis set)

Timepoint	WHO Modified Analgesic Ladder Score-Drug class	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Cycle 42	Total non-missing	n	2	2
	0-No Analgesia	n (%)	1 (50.0)	2 (100)
	1-Non-opioids	n (%)	0	0
	2-Neuropathic/other non-typical pain medications	n (%)	1 (50.0)	0
	3-Weak opioids	n (%)	0	0
	4-Strong opioids	n (%)	0	0

Any Chronic PN pain medication recorded in the daily e-Diary is scored using the WHO Modified Analgesic Ladder (see statistical analysis plan). Subjects are counted in the Drug class of the highest score recorded in 28-day cycle regardless of the frequency. Percentages are based on the number of subjects with non-missing data at the corresponding visit (i.e., Total non-missing). n Number of subjects per category. N Number of subjects in treatment group. PN Plexiform Neurofibroma. WHO Global World Health Organization. WHODrug Global B3-format Sep 2024. Full analysis set - subjects randomised to studyintervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff249.sas
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1.4 Endpunkt Tägliche Funktionsfähigkeit anhand PII-pNF – Veränderung zu Baseline

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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	70		72	
	Mean	2.638		2.417	
	SD	1.6039		1.6812	
	Min	0.00		0.00	
	Q1	1.333		0.917	
	Median	2.958		2.390	
	Q3	3.818		3.917	
	Max	6.00		5.55	
Cycle 1, Day 28	n	70	69	74	72
	Mean	2.098	-0.547	1.780	-0.623
	SD	1.4916	0.9791	1.4280	0.8855
	Min	0.00	-3.25	0.00	-3.30
	Q1	0.833	-1.000	0.333	-1.129
	Median	2.129	-0.636	1.636	-0.542
	Q3	3.182	0.000	2.909	0.000
	Max	5.50	1.58	5.25	1.90

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 2, Day 28	n	66	65	74	72
	Mean	1.834	-0.824	1.822	-0.578
	SD	1.5255	1.2217	1.5719	1.0791
	Min	0.00	-3.75	0.00	-3.80
	Q1	0.417	-1.750	0.417	-1.170
	Median	1.708	-0.697	1.333	-0.458
	Q3	2.917	0.000	2.917	0.042
	Max	6.00	2.18	5.50	1.92
Cycle 4, Day 28	n	65	64	69	67
	Mean	1.705	-1.014	1.783	-0.612
	SD	1.3758	1.1805	1.4764	1.0573
	Min	0.00	-3.42	0.00	-3.71
	Q1	0.667	-1.761	0.500	-1.167
	Median	1.583	-0.917	1.417	-0.439
	Q3	2.750	0.000	2.917	0.000
	Max	6.00	1.58	5.42	1.98

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 6, Day 28	n	64	63	68	66
	Mean	1.789	-0.947	1.706	-0.664
	SD	1.4500	1.1597	1.4500	1.3008
	Min	0.00	-3.66	0.00	-3.92
	Q1	0.610	-1.917	0.216	-1.250
	Median	1.458	-0.735	1.500	-0.417
	Q3	2.655	0.000	2.826	0.000
	Max	6.00	1.51	4.82	2.57
Cycle 8, Day 28	n	60	59	66	64
	Mean	1.743	-0.969	1.768	-0.493
	SD	1.4592	1.2838	1.4726	1.2526
	Min	0.00	-4.08	0.00	-3.98
	Q1	0.564	-1.818	0.182	-1.208
	Median	1.292	-1.083	1.875	-0.250
	Q3	2.917	0.000	2.917	0.000
	Max	5.50	1.50	4.92	2.75

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 10, Day 28	n	61	60	66	64
	Mean	1.660	-1.033	1.732	-0.509
	SD	1.4775	1.1934	1.5596	1.1552
	Min	0.00	-4.00	0.00	-4.33
	Q1	0.500	-1.803	0.250	-0.996
	Median	1.083	-0.697	1.455	-0.174
	Q3	2.833	0.000	3.000	0.125
	Max	6.00	0.96	5.36	1.75
Cycle 12, Day 28	n	61	60	64	62
	Mean	1.723	-0.986	1.811	-0.420
	SD	1.5029	1.3327	1.5220	1.2699
	Min	0.00	-3.83	0.00	-3.50
	Q1	0.455	-1.973	0.174	-1.000
	Median	1.545	-0.708	1.864	-0.254
	Q3	2.917	0.000	3.000	0.000
	Max	5.75	1.33	4.82	2.58

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 16, Day 28	n	54	53	63	61
	Mean	1.641	-1.007	1.516	-0.817
	SD	1.4565	1.2969	1.4289	1.5368
	Min	0.00	-4.33	0.00	-4.82
	Q1	0.333	-1.727	0.000	-1.333
	Median	1.394	-0.750	1.083	-0.750
	Q3	2.583	0.000	2.667	0.000
	Max	5.50	1.09	4.92	2.58
Cycle 20, Day 28	n	54	53	60	58
	Mean	1.774	-0.912	1.448	-0.853
	SD	1.6088	1.5406	1.3631	1.5846
	Min	0.00	-4.42	0.00	-5.09
	Q1	0.364	-1.917	0.000	-1.636
	Median	1.625	-0.750	1.208	-0.739
	Q3	2.750	0.000	2.667	0.000
	Max	6.00	2.64	5.58	3.67

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 24, Day 28	n	44	43	51	49
	Mean	1.600	-0.976	1.136	-0.919
	SD	1.3533	1.4402	1.1692	1.4033
	Min	0.00	-4.09	0.00	-4.91
	Q1	0.523	-2.167	0.000	-1.492
	Median	1.348	-0.917	0.636	-0.553
	Q3	2.693	0.053	2.167	0.000
	Max	4.67	2.27	3.50	1.36
Cycle 30, Day 28	n	17	17	26	25
	Mean	1.787	-0.589	0.814	-0.941
	SD	1.5465	1.3918	0.9848	1.4383
	Min	0.00	-2.25	0.00	-5.36
	Q1	0.545	-1.545	0.000	-1.583
	Median	1.250	-0.977	0.458	-0.333
	Q3	3.000	0.000	1.500	0.000
	Max	5.50	2.91	3.83	0.42

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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Final DCO PSC
Table 14.2.12.1 PII-pNF pain interference total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 36, Day 28	n	6	6	7	7
	Mean	2.114	-0.895	1.345	-0.731
	SD	1.8733	0.9533	1.7869	0.9846
	Min	0.00	-2.18	0.00	-2.36
	Q1	0.083	-1.333	0.000	-1.500
	Median	2.348	-0.958	0.583	-0.167
	Q3	3.818	-0.667	2.250	-0.083
	Max	4.08	0.73	4.83	0.33
Cycle 42, Day 28	n	1	1	2	2
	Mean	3.583	-1.833	1.375	-0.723
	SD	NC	NC	1.9445	2.3195
	Min	3.58	-1.83	0.00	-2.36
	Q1	3.583	-1.833	0.000	-2.364
	Median	3.583	-1.833	1.375	-0.723
	Q3	3.583	-1.833	2.750	0.917
	Max	3.58	-1.83	2.75	0.92

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PII-pNF pain interference total score (range 0 to 6) indicates more pain interference. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PII-pNF Pain interference index - plexiform neurofibroma.
Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.NC Not calculated.
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1.5 Endpunkt Gesundheitszustand anhand EQ-5D VAS – Veränderung zu Baseline

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Table 14.2.15.4 EQ-VAS score over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	70		72	
	Mean	63.5		62.1	
	SD	19.06		21.18	
	Min	30		1	
	Q1	49.0		48.0	
	Median	60.0		65.0	
	Q3	79.0		78.5	
	Max	100		98	
Cycle 2, Day 28	n	67	66	74	72
	Mean	67.5	3.3	67.6	5.3
	SD	19.37	16.12	19.18	17.24
	Min	21	-30	1	-40
	Q1	50.0	-7.0	50.0	-5.0
	Median	70.0	3.0	70.0	8.5
	Q3	80.0	11.0	84.0	15.0
	Max	100	38	100	50

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement. EQ-VAS EuroQol visual analogue scale. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff268.sas
Executed: 2025-06-24T172820

Study Code: D134BC00001 Phase III Page 2 of 6
Final DCO PSC
Table 14.2.15.4 EQ-VAS score over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 4, Day 28	n	65	64	69	67
	Mean	68.2	4.7	67.4	4.9
	SD	20.20	20.73	19.55	16.37
	Min	9	-70	25	-34
	Q1	60.0	-5.0	55.0	-3.0
	Median	70.0	5.0	70.0	4.0
	Q3	84.0	17.5	80.0	13.0
	Max	100	41	100	62
Cycle 8, Day 28	n	61	60	67	65
	Mean	66.0	2.7	65.2	2.5
	SD	21.26	22.23	20.88	15.49
	Min	14	-69	11	-50
	Q1	51.0	-9.5	50.0	-5.0
	Median	70.0	4.0	66.0	0.0
	Q3	80.0	17.5	85.0	10.0
	Max	100	54	98	40

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement. EQ-VAS EuroQol visual analogue scale. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff268.sas
Executed: 2025-06-24T172820

Study Code: D134BC00001 Phase III Page 3 of 6
Final DCO PSC
Table 14.2.15.4 EQ-VAS score over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 12, Day 28	n	61	60	64	62
	Mean	70.9	7.0	68.6	6.1
	SD	19.33	18.95	18.75	15.71
	Min	19	-53	8	-30
	Q1	60.0	-2.5	59.0	-5.0
	Median	75.0	8.5	71.0	4.0
	Q3	81.0	17.5	85.0	11.0
	Max	100	45	96	49
Cycle 16, Day 28	n	54	53	63	61
	Mean	72.9	10.5	71.3	9.4
	SD	17.20	15.04	18.76	17.72
	Min	21	-30	25	-22
	Q1	61.0	1.0	59.0	-1.0
	Median	75.0	10.0	75.0	9.0
	Q3	86.0	20.0	89.0	20.0
	Max	100	44	100	60

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement. EQ-VAS EuroQol visual analogue scale. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff268.sas
Executed: 2025-06-24T172820

Study Code: D134BC00001 Phase III Page 4 of 6
Final DCO PSC
Table 14.2.15.4 EQ-VAS score over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 20, Day 28	n	54	53	59	57
	Mean	68.8	5.6	73.4	10.0
	SD	19.95	16.80	17.54	19.13
	Min	20	-50	20	-21
	Q1	56.0	-2.0	61.0	-2.0
	Median	74.5	5.0	75.0	6.0
	Q3	80.0	14.0	90.0	17.0
	Max	100	45	97	60
Cycle 24, Day 28	n	44	43	51	49
	Mean	72.1	10.9	72.8	8.3
	SD	18.13	15.62	19.63	20.43
	Min	19	-29	31	-39
	Q1	63.0	1.0	60.0	-2.0
	Median	75.0	10.0	78.0	5.0
	Q3	87.0	20.0	90.0	17.0
	Max	95	55	95	60

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement. EQ-VAS EuroQol visual analogue scale. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff268.sas
Executed: 2025-06-24T172820

Study Code: D134BC00001 Phase III Page 5 of 6
Final DCO PSC
Table 14.2.15.4 EQ-VAS score over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 30, Day 28	n	18	18	26	25
	Mean	68.2	4.6	72.5	9.4
	SD	17.95	15.52	21.57	18.61
	Min	39	-17	30	-24
	Q1	53.0	-6.0	60.0	-2.0
	Median	74.0	4.0	79.5	8.0
	Q3	81.0	13.0	90.0	21.0
	Max	98	45	99	55
Cycle 36, Day 28	n	6	6	7	7
	Mean	63.8	4.2	64.4	9.9
	SD	20.11	11.48	21.08	19.53
	Min	31	-9	30	-15
	Q1	50.0	-7.0	43.0	-10.0
	Median	71.0	3.5	68.0	12.0
	Q3	80.0	14.0	80.0	24.0
	Max	80	20	90	40

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement. EQ-VAS EuroQol visual analogue scale. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff268.sas
Executed: 2025-06-24T172820

Study Code: D134BC00001 Phase III Page 6 of 6
Final DCO PSC
Table 14.2.15.4 EQ-VAS score over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 42, Day 28	n	1	1	2	2
	Mean	30.0	0.0	75.5	30.5
	SD	NC	NC	0.71	7.78
	Min	30	0	75	25
	Q1	30.0	0.0	75.0	25.0
	Median	30.0	0.0	75.5	30.5
	Q3	30.0	0.0	76.0	36.0
	Max	30	0	76	36

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher EQ-VAS score (range from 0 to 100) indicates better health status. A positive change from baseline indicates an improvement. EQ-VAS EuroQol visual analogue scale. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff268.sas
Executed: 2025-06-24T172820

1.6 Endpunkt Körperliche Funktionsfähigkeit anhand PROMIS – Veränderung zu Baseline

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.2.13.1 PROMIS Physical Function scores over time: actual value and change from Baseline (Full analysis set)

PFA01-Total Score

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	70		72	
	Mean	10.2		10.5	
	SD	2.61		3.11	
	Min	5		3	
	Q1	8.0		8.0	
	Median	10.0		11.0	
	Q3	12.0		13.0	
	Max	15		15	
Cycle 2, Day 28	n	67	66	74	72
	Mean	11.0	0.7	11.4	0.9
	SD	2.43	2.22	3.16	1.85
	Min	5	-6	3	-4
	Q1	9.0	0.0	10.0	0.0
	Median	12.0	1.0	11.0	1.0
	Q3	13.0	2.0	15.0	2.0
	Max	15	7	15	6

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PROMIS Patient-Reported Outcomes Measurement Information System. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention. NC Not calculated.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff260_new.sas
Executed: 2025-06-24T172805

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.2.13.1 PROMIS Physical Function scores over time: actual value and change from Baseline (Full analysis set)

PFA01-Total Score

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 4, Day 28	n	65	64	69	67
	Mean	11.3	1.2	11.3	0.7
	SD	2.34	2.12	3.27	1.76
	Min	6	-4	3	-3
	Q1	10.0	0.0	10.0	0.0
	Median	12.0	1.0	11.0	0.0
	Q3	13.0	3.0	15.0	2.0
	Max	15	6	15	5
Cycle 8, Day 28	n	61	60	67	65
	Mean	11.3	1.2	11.4	0.6
	SD	2.51	1.95	3.19	1.93
	Min	6	-2	3	-4
	Q1	9.0	0.0	9.0	0.0
	Median	11.0	1.0	12.0	1.0
	Q3	13.0	3.0	15.0	1.0
	Max	15	7	15	8

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PROMIS Patient-Reported Outcomes Measurement Information System. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention. NC Not calculated.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff260_new.sas
Executed: 2025-06-24T172805

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.2.13.1 PROMIS Physical Function scores over time: actual value and change from Baseline (Full analysis set)

PFA01-Total Score

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 12, Day 28	n	61	60	64	62
	Mean	11.0	0.9	11.5	0.7
	SD	2.66	2.38	3.29	1.96
	Min	6	-5	3	-4
	Q1	9.0	-0.5	10.0	0.0
	Median	11.0	1.0	11.5	0.0
	Q3	13.0	3.0	15.0	2.0
	Max	15	6	15	8
Cycle 16, Day 28	n	54	53	63	61
	Mean	11.3	1.2	11.8	1.2
	SD	2.70	2.40	2.98	2.00
	Min	6	-4	3	-4
	Q1	9.0	0.0	10.0	0.0
	Median	11.5	1.0	12.0	1.0
	Q3	14.0	2.0	15.0	2.0
	Max	15	8	15	8

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PROMIS Patient-Reported Outcomes Measurement Information System. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention. NC Not calculated.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff260_new.sas
Executed: 2025-06-24T172805

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.2.13.1 PROMIS Physical Function scores over time: actual value and change from Baseline (Full analysis set)

PFA01-Total Score

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 20, Day 28	n	54	53	60	58
	Mean	10.8	0.6	11.7	1.0
	SD	2.78	2.39	2.95	2.40
	Min	5	-7	3	-5
	Q1	9.0	-1.0	10.0	0.0
	Median	11.0	0.0	12.0	1.0
	Q3	13.0	2.0	15.0	2.0
	Max	15	6	15	8
Cycle 24, Day 28	n	44	43	51	49
	Mean	11.3	0.8	11.8	0.7
	SD	2.49	2.19	2.94	2.46
	Min	6	-3	4	-5
	Q1	9.5	-1.0	10.0	0.0
	Median	12.0	0.0	12.0	0.0
	Q3	13.0	2.0	15.0	2.0
	Max	15	5	15	9

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PROMIS Patient-Reported Outcomes Measurement Information System. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention. NC Not calculated.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff260_new.sas
Executed: 2025-06-24T172805

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.2.13.1 PROMIS Physical Function scores over time: actual value and change from Baseline (Full analysis set)

PFA01-Total Score

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 30, Day 28	n	17	17	26	25
	Mean	11.1	0.5	12.3	1.2
	SD	2.42	2.40	3.15	2.89
	Min	5	-4	6	-4
	Q1	10.0	0.0	10.0	0.0
	Median	11.0	0.0	14.0	1.0
	Q3	12.0	3.0	15.0	2.0
	Max	15	4	15	9
Cycle 36, Day 28	n	6	6	7	7
	Mean	10.5	2.2	11.7	0.7
	SD	2.59	0.98	2.29	3.82
	Min	6	1	8	-4
	Q1	9.0	1.0	10.0	-1.0
	Median	11.5	2.5	12.0	0.0
	Q3	12.0	3.0	13.0	3.0
	Max	13	3	15	8

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PROMIS Patient-Reported Outcomes Measurement Information System. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention. NC Not calculated.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff260_new.sas
Executed: 2025-06-24T172805

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.2.13.1 PROMIS Physical Function scores over time: actual value and change from Baseline (Full analysis set)

PFA01-Total Score

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 42, Day 28	n	1	1	2	2
	Mean	9.0	3.0	14.0	5.0
	SD	NC	NC	1.41	4.24
	Min	9	3	13	2
	Q1	9.0	3.0	13.0	2.0
	Median	9.0	3.0	14.0	5.0
	Q3	9.0	3.0	15.0	8.0
	Max	9	3	15	8

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. A higher PROMIS score indicates a better physical functioning. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. PROMIS Patient-Reported Outcomes Measurement Information System. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention. NC Not calculated.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff260_new.sas
Executed: 2025-06-24T172805

2 Endpunktkategorie Gesundheitsbezogene Lebensqualität

2.1 Endpunkt Gesundheitsbezogene Lebensqualität anhand PlexiQoL – Veränderung zu Baseline

Study Code: D134BC00001 Phase III Page 1 of 6
Final DCO PSC
Table 14.2.3.1 PlexiQoL total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	70		72	
	Mean	9.3		8.1	
	SD	4.73		4.10	
	Min	0		0	
	Q1	6.0		5.0	
	Median	10.0		8.0	
	Q3	13.0		11.0	
	Max	17		18	
Cycle 2, Day 28	n	67	66	74	72
	Mean	8.2	-1.0	7.2	-0.7
	SD	5.00	3.23	4.45	2.99
	Min	0	-12	0	-10
	Q1	3.0	-2.0	4.0	-3.0
	Median	8.0	-1.0	7.0	-1.0
	Q3	12.0	1.0	10.0	1.5
	Max	17	6	18	7

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >3 items are missing, score is not derived. A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff262.sas
Executed: 2025-06-24T172810

Study Code: D134BC00001 Phase III Page 2 of 6
Final DCO PSC
Table 14.2.3.1 PlexiQoL total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 4, Day 28	n	65	64	69	67
	Mean	8.6	-1.0	7.0	-1.1
	SD	4.98	3.31	4.44	2.48
	Min	0	-11	0	-7
	Q1	5.0	-3.0	3.0	-3.0
	Median	9.0	-1.0	7.0	-1.0
	Q3	12.0	1.0	10.0	0.0
	Max	18	5	18	6
Cycle 8, Day 28	n	61	60	67	65
	Mean	8.6	-1.0	7.2	-0.8
	SD	4.87	3.54	5.02	3.49
	Min	0	-13	0	-9
	Q1	5.0	-3.0	3.0	-3.0
	Median	9.0	-0.5	7.0	-1.0
	Q3	13.0	1.0	10.0	1.0
	Max	18	9	18	8

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >3 items are missing, score is not derived. A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff262.sas
Executed: 2025-06-24T172810

Study Code: D134BC00001 Phase III Page 3 of 6
Final DCO PSC
Table 14.2.3.1 PlexiQoL total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 12, Day 28	n	61	60	64	62
	Mean	8.8	-0.7	7.6	-0.4
	SD	5.00	3.30	4.88	3.52
	Min	0	-8	0	-10
	Q1	4.0	-3.0	4.0	-3.0
	Median	9.0	-1.0	7.0	-1.0
	Q3	12.0	1.5	11.0	2.0
	Max	18	8	18	7
Cycle 16, Day 28	n	54	53	63	61
	Mean	8.6	-0.9	7.5	-0.4
	SD	5.20	3.37	5.04	3.86
	Min	0	-8	0	-10
	Q1	4.0	-3.0	2.0	-3.0
	Median	9.0	-1.0	8.0	0.0
	Q3	13.0	1.0	11.0	2.0
	Max	18	7	18	7

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >3 items are missing, score is not derived. A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.3.1 PlexiQoL total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 20, Day 28	n	54	53	60	58
	Mean	8.9	-0.8	7.2	-0.8
	SD	4.78	3.77	4.95	3.52
	Min	0	-9	0	-10
	Q1	6.0	-2.0	3.5	-3.0
	Median	9.0	-1.0	6.0	-1.0
	Q3	12.0	0.0	11.0	2.0
	Max	17	8	18	8
Cycle 24, Day 28	n	44	43	51	49
	Mean	9.1	-0.4	6.8	-0.7
	SD	5.32	4.07	4.86	4.45
	Min	0	-10	0	-16
	Q1	4.5	-3.0	3.0	-3.0
	Median	10.0	0.0	6.0	-1.0
	Q3	13.5	2.0	10.0	1.0
	Max	17	11	18	9

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >3 items are missing, score is not derived. A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/eff262.sas
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Table 14.2.3.1 PlexiQoL total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 30, Day 28	n	17	17	26	25
	Mean	8.5	-0.4	7.0	-0.2
	SD	5.11	3.66	4.57	3.90
	Min	0	-10	0	-11
	Q1	6.0	-1.0	4.0	-2.0
	Median	10.0	0.0	6.5	0.0
	Q3	11.0	1.0	9.0	2.0
	Max	18	4	16	7
Cycle 36, Day 28	n	6	6	7	7
	Mean	8.2	0.8	7.7	0.3
	SD	5.00	3.66	5.77	4.23
	Min	0	-2	0	-7
	Q1	6.0	-1.0	4.0	-3.0
	Median	8.5	-0.5	6.0	1.0
	Q3	12.0	1.0	13.0	3.0
	Max	14	8	17	6

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >3 items are missing, score is not derived. A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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Table 14.2.3.1 PlexiQoL total scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 42, Day 28	n	1	1	2	2
	Mean	12.0	-2.0	3.5	-6.5
	SD	NC	NC	4.95	0.71
	Min	12	-2	0	-7
	Q1	12.0	-2.0	0.0	-7.0
	Median	12.0	-2.0	3.5	-6.5
	Q3	12.0	-2.0	7.0	-6.0
	Max	12	-2	7	-6

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >3 items are missing, score is not derived. A higher PlexiQoL total score indicates a worse quality of life. A negative change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PlexiQoL Plexiform Neurofibroma Quality of Life scale. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Full analysis set - subjects randomised to study intervention.
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2.2 Endpunkt Gesundheitsbezogene Lebensqualität anhand PedsQL – Veränderung zu Baseline

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Final DCO PSC
Table 14.2.14.1 PedsQL skin sensations scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Baseline	n	71		72	
	Mean	59.977		61.111	
	SD	25.2220		28.1817	
	Min	0.00		0.00	
	Q1	41.667		41.667	
	Median	58.333		58.333	
	Q3	75.000		87.500	
	Max	100.00		100.00	
Cycle 2, Day 28	n	67	67	74	72
	Mean	62.562	3.109	66.554	6.250
	SD	26.0864	22.9751	23.5901	19.3169
	Min	0.00	-75.00	8.33	-33.33
	Q1	41.667	-8.333	50.000	-8.333
	Median	66.667	8.333	66.667	4.167
	Q3	83.333	16.667	83.333	16.667
	Max	100.00	58.33	100.00	66.67

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >50% items are missing, score is not derived. If <=50% items are missing, missing items are imputed with the mean of completed items. A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.14.1 PedsQL skin sensations scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 4, Day 28	n	65	65	69	67
	Mean	64.615	5.897	67.271	5.970
	SD	23.5256	20.7667	23.3228	21.6047
	Min	0.00	-50.00	16.67	-50.00
	Q1	50.000	-8.333	50.000	-8.333
	Median	58.333	8.333	66.667	8.333
	Q3	83.333	16.667	83.333	16.667
	Max	100.00	58.33	100.00	66.67
Cycle 8, Day 28	n	61	61	67	65
	Mean	62.978	4.645	68.035	5.897
	SD	25.3460	21.4910	24.5154	19.1917
	Min	0.00	-50.00	16.67	-50.00
	Q1	50.000	-8.333	50.000	0.000
	Median	66.667	0.000	66.667	0.000
	Q3	83.333	16.667	91.667	16.667
	Max	100.00	50.00	100.00	58.33

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >50% items are missing, score is not derived. If <=50% items are missing, missing items are imputed with the mean of completed items. A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.14.1 PedsQL skin sensations scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 12, Day 28	n	61	61	64	62
	Mean	65.437	6.011	69.141	6.586
	SD	26.3451	20.7571	24.2015	19.6240
	Min	0.00	-41.67	8.33	-33.33
	Q1	50.000	-8.333	50.000	0.000
	Median	66.667	8.333	75.000	0.000
	Q3	91.667	16.667	87.500	16.667
	Max	100.00	75.00	100.00	75.00
Cycle 16, Day 28	n	54	54	63	61
	Mean	63.889	3.549	68.783	7.514
	SD	25.3384	22.1133	25.8359	23.0089
	Min	0.00	-41.67	0.00	-50.00
	Q1	50.000	-8.333	50.000	-8.333
	Median	66.667	0.000	66.667	0.000
	Q3	83.333	16.667	91.667	25.000
	Max	100.00	50.00	100.00	75.00

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >50% items are missing, score is not derived. If <=50% items are missing, missing items are imputed with the mean of completed items. A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.14.1 PedsQL skin sensations scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 20, Day 28	n	54	54	60	58
	Mean	66.204	6.944	70.000	7.040
	SD	25.8714	21.0912	21.7631	22.2844
	Min	0.00	-50.00	16.67	-50.00
	Q1	41.667	-8.333	50.000	-8.333
	Median	66.667	8.333	75.000	0.000
	Q3	83.333	25.000	83.333	25.000
	Max	100.00	50.00	100.00	83.33
Cycle 24, Day 28	n	44	44	51	49
	Mean	67.235	7.576	71.078	5.612
	SD	23.7339	23.7625	24.2872	22.6556
	Min	8.33	-50.00	16.67	-50.00
	Q1	50.000	-4.167	50.000	0.000
	Median	70.833	4.167	75.000	0.000
	Q3	83.333	25.000	91.667	16.667
	Max	100.00	50.00	100.00	75.00

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >50% items are missing, score is not derived. If <=50% items are missing, missing items are imputed with the mean of completed items. A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.14.1 PedsQL skin sensations scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 30, Day 28	n	17	17	26	25
	Mean	65.686	2.451	76.603	6.333
	SD	28.5473	23.5269	22.2385	27.3523
	Min	0.00	-41.67	33.33	-41.67
	Q1	50.000	-8.333	58.333	-8.333
	Median	75.000	0.000	79.167	0.000
	Q3	83.333	8.333	100.000	16.667
	Max	100.00	50.00	100.00	91.67
Cycle 36, Day 28	n	6	6	7	7
	Mean	62.500	2.778	80.952	0.000
	SD	41.4159	23.3730	20.2498	15.9571
	Min	0.00	-41.67	50.00	-25.00
	Q1	33.333	0.000	66.667	-16.667
	Median	70.833	8.333	83.333	0.000
	Q3	100.000	16.667	100.000	16.667
	Max	100.00	25.00	100.00	16.67

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >50% items are missing, score is not derived. If <=50% items are missing, missing items are imputed with the mean of completed items. A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
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Final DCO PSC
Table 14.2.14.1 PedsQL skin sensations scores over time: actual value and change from Baseline (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Statistic	Actual value	Change from baseline	Actual value	Change from baseline
Cycle 42, Day 28	n	1	1	2	2
	Mean	33.333	-8.333	100.000	25.000
	SD	NC	NC	0.0000	11.7851
	Min	33.33	-8.33	100.00	16.67
	Q1	33.333	-8.333	100.000	16.667
	Median	33.333	-8.333	100.000	25.000
	Q3	33.333	-8.333	100.000	33.333
	Max	33.33	-8.33	100.00	33.33

Baseline is defined as the last result obtained prior to the start of the randomised period. Post-baseline score is derived from closest assessment to scheduled visit date. If >50% items are missing, score is not derived. If <=50% items are missing, missing items are imputed with the mean of completed items. A higher PedsQL score (range 0 to 100) is better. A positive change from baseline indicates an improvement. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. NC Not calculated. PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation. Full analysis set - subjects randomised to study intervention.
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3 Endpunktkategorie Sicherheit

3.1 Endpunkt Unerwünschte Ereignisse (UE)

3.1.1 Gesamtraten UE

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Final DCO PSC
Table 14.3.2.1.2 Number of subjects with treatment emergent adverse events in any category (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
AE category	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Any AE	71 (100) [2834.2]	63 (95.5) [805.7]	134 (97.8) [1297.9]
Any AE possibly related to study intervention [b]	68 (95.8) [852.6]	59 (89.4) [404.2]	127 (92.7) [562.7]
Any AE of CTCAE grade 3 or higher	33 (46.5) [34.7]	18 (27.3) [26.2]	51 (37.2) [31.1]
Any AE of CTCAE grade 3 or higher, possibly related to study intervention [b]	21 (29.6) [19.1]	10 (15.2) [12.9]	31 (22.6) [16.5]
Any AE with outcome of death	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Any AE with outcome of death, possibly related to study intervention [b]	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories. [b] As assessed by the investigator. [c] Action taken either a drug interruption and/or a dose reduction. [d] Significant AEs, other than SAEs and those AEs leading to discontinuation of study intervention, which are of particular clinical importance, are identified and classified as other significant AEs.
Includes only AEs that are treatment emergent during the on-selumetinib period. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae201.sas
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Final DCO PSC
Table 14.3.2.1.2 Number of subjects with treatment emergent adverse events in any category (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
AE category	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Any SAE (including events with outcome of death)	14 (19.7) [11.5]	10 (15.2) [12.6]	24 (17.5) [11.9]
Any SAE (including events with outcome of death), possibly related to study intervention [b]	5 (7.0) [3.8]	1 (1.5) [1.2]	6 (4.4) [2.8]
Any SAE leading to discontinuation of study intervention	6 (8.5) [4.5]	1 (1.5) [1.2]	7 (5.1) [3.2]
Any SAE leading to discontinuation of study intervention, possibly related to study intervention [b]	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Any AE leading to discontinuation of study intervention	11 (15.5) [8.4]	2 (3.0) [2.4]	13 (9.5) [6.0]
Any AE leading to discontinuation of study intervention, possibly related to study intervention [b]	6 (8.5) [4.6]	1 (1.5) [1.2]	7 (5.1) [3.2]

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories. [b] As assessed by the investigator. [c] Action taken either a drug interruption and/or a dose reduction. [d] Significant AEs, other than SAEs and those AEs leading to discontinuation of study intervention, which are of particular clinical importance, are identified and classified as other significant AEs.
Includes only AEs that are treatment emergent during the on-selumetinib period. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.1.2 Number of subjects with treatment emergent adverse events in any category (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
AE category	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Any AE leading to dose interruption of study intervention	21 (29.6) [19.5]	26 (39.4) [40.5]	47 (34.3) [27.3]
Any AE leading to dose reduction of study intervention	20 (28.2) [20.1]	11 (16.7) [14.6]	31 (22.6) [17.7]
Any AE leading to dose modification [c]	34 (47.9) [39.7]	28 (42.4) [46.1]	62 (45.3) [42.3]
Any AEs of special interest	48 (67.6) [95.8]	37 (56.1) [74.9]	85 (62.0) [85.4]
Any other significant AEs [d]	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories. [b] As assessed by the investigator. [c] Action taken either a drug interruption and/or a dose reduction. [d] Significant AEs, other than SAEs and those AEs leading to discontinuation of study intervention, which are of particular clinical importance, are identified and classified as other significant AEs.
Includes only AEs that are treatment emergent during the on-selumetinib period. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae201.sas
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3.1.2 UE nach System Organ Class (SOC) und Preferred Term (PT)

3.1.2.1 UE jeglichen Schweregrads

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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Subjects with any AE	71 (100) [2834.2]	63 (95.5) [805.7]	134 (97.8) [1297.9]
Infections and infestations	45 (63.4) [67.1]	30 (45.5) [51.6]	75 (54.7) [59.9]
Appendicitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Bacteriuria	3 (4.2) [2.3]	2 (3.0) [2.4]	5 (3.6) [2.4]
Bronchitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
COVID-19	13 (18.3) [11.3]	3 (4.5) [3.7]	16 (11.7) [8.1]
Cellulitis	4 (5.6) [3.1]	2 (3.0) [2.4]	6 (4.4) [2.8]
Conjunctivitis	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Cystitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Folliculitis	4 (5.6) [3.1]	2 (3.0) [2.4]	6 (4.4) [2.8]
Fungal skin infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Furuncle	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Gastroenteritis	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Gastroenteritis viral	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Gastrointestinal infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Gingivitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Herpes simplex	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Herpes virus infection	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Herpes zoster	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Hordeolum	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Influenza	7 (9.9) [5.5]	6 (9.1) [7.5]	13 (9.5) [6.3]
Kidney infection	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Lip infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Lower respiratory tract infection	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Nasopharyngitis	3 (4.2) [2.4]	1 (1.5) [1.2]	4 (2.9) [1.9]
Onychomycosis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Oral candidiasis	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Oral herpes	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Parainfluenzae virus infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Paronychia	17 (23.9) [15.2]	12 (18.2) [15.9]	29 (21.2) [15.5]
Periodontitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Pharyngitis	2 (2.8) [1.5]	3 (4.5) [3.7]	5 (3.6) [2.4]
Pneumonia	2 (2.8) [1.5]	3 (4.5) [3.6]	5 (3.6) [2.4]
Pneumonia aspiration	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Rash pustular	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Respiratory tract infection	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Sepsis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Septic shock	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Sinusitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Skin infection	3 (4.2) [2.3]	1 (1.5) [1.2]	4 (2.9) [1.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Staphylococcal skin infection	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Tinea cruris	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tinea pedis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tonsillitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Tracheitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tracheobronchitis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Upper respiratory tract infection	8 (11.3) [6.5]	3 (4.5) [3.6]	11 (8.0) [5.3]
Urinary tract infection	6 (8.5) [4.7]	1 (1.5) [1.2]	7 (5.1) [3.3]
Vaginal infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Viral infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (4.2) [2.3]	1 (1.5) [1.2]	4 (2.9) [1.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Clear cell renal cell carcinoma	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neurofibrosarcoma	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neurofibrosarcoma recurrent	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tumour haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Blood and lymphatic system disorders	9 (12.7) [7.4]	12 (18.2) [16.8]	21 (15.3) [10.9]
Anaemia	6 (8.5) [4.8]	9 (13.6) [12.2]	15 (10.9) [7.6]
Eosinopenia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Eosinophilia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Lymphopenia	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Normocytic anaemia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Thrombocytopenia	0	2 (3.0) [2.4]	2 (1.5) [0.9]
Endocrine disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Hyperparathyroidism secondary	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Metabolism and nutrition disorders	8 (11.3) [6.6]	10 (15.2) [13.4]	18 (13.1) [9.2]
Decreased appetite	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Hypermagnesaemia	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Hyperphosphataemia	2 (2.8) [1.5]	3 (4.5) [3.6]	5 (3.6) [2.3]
Hyperuricaemia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Hypoalbuminaemia	1 (1.4) [0.8]	3 (4.5) [3.6]	4 (2.9) [1.9]
Hypokalaemia	2 (2.8) [1.5]	4 (6.1) [5.0]	6 (4.4) [2.8]
Hypomagnesaemia	0	2 (3.0) [2.4]	2 (1.5) [0.9]
Hypophosphataemia	0	3 (4.5) [3.7]	3 (2.2) [1.4]
Vitamin D deficiency	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Psychiatric disorders	10 (14.1) [8.2]	1 (1.5) [1.2]	11 (8.0) [5.4]
Anxiety	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Depressed mood	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Depression	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Euphoric mood	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Insomnia	5 (7.0) [3.9]	0	5 (3.6) [2.4]
Irritability	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Libido decreased	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Mood swings	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nicotine dependence	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Psychiatric decompensation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Self-induced vomiting	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nervous system disorders	22 (31.0) [22.6]	11 (16.7) [14.7]	33 (24.1) [19.1]
Brain fog	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Disturbance in attention	2 (2.8) [1.5]	0	2 (1.5) [0.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Dizziness	5 (7.0) [3.9]	1 (1.5) [1.2]	6 (4.4) [2.8]
Dizziness postural	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Dysaesthesia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Dyskinesia	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Headache	10 (14.1) [8.5]	5 (7.6) [6.2]	15 (10.9) [7.5]
Hyposmia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Loss of consciousness	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Migraine	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neuropathy peripheral	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Nystagmus	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Paraesthesia	5 (7.0) [3.9]	3 (4.5) [3.7]	8 (5.8) [3.8]
Paraparesis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Seizure	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Syncope	3 (4.2) [2.3]	1 (1.5) [1.2]	4 (2.9) [1.9]
Taste disorder	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tremor	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Eye disorders	15 (21.1) [13.4]	7 (10.6) [8.6]	22 (16.1) [11.4]
Asthenopia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Blepharitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Cataract	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Conjunctival hyperaemia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Dry eye	2 (2.8) [1.6]	0	2 (1.5) [0.9]
Eye pain	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Eye swelling	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Eyelid oedema	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Glaucoma	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Mydriasis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Orbital swelling	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Periorbital oedema	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Pupillary reflex impaired	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Serous retinal detachment	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Ulcerative keratitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Vision blurred	3 (4.2) [2.3]	2 (3.0) [2.4]	5 (3.6) [2.3]
Visual acuity reduced	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Vitreous floaters	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Xerophthalmia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ear and labyrinth disorders	6 (8.5) [4.8]	1 (1.5) [1.2]	7 (5.1) [3.4]
Deafness bilateral	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Deafness neurosensory	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Deafness unilateral	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ear pain	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Vertigo	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Vertigo positional	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Cardiac disorders	4 (5.6) [3.1]	2 (3.0) [2.4]	6 (4.4) [2.8]
Angina pectoris	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Mitral valve incompetence	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Palpitations	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Pulmonary valve incompetence	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Tachycardia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ventricular arrhythmia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Vascular disorders	9 (12.7) [7.4]	1 (1.5) [1.2]	10 (7.3) [4.9]
Deep vein thrombosis	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Haematoma	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Hypertension	4 (5.6) [3.1]	0	4 (2.9) [1.9]
Lymphoedema	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Orthostatic hypotension	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Peripheral coldness	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Peripheral venous disease	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Superficial vein thrombosis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Respiratory, thoracic and mediastinal disorders	19 (26.8) [17.6]	7 (10.6) [8.8]	26 (19.0) [13.9]
Aphonia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Cough	6 (8.5) [4.8]	1 (1.5) [1.2]	7 (5.1) [3.4]
Dyspnoea	4 (5.6) [3.2]	0	4 (2.9) [1.9]
Epistaxis	0	2 (3.0) [2.4]	2 (1.5) [0.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Nasal congestion	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nasal dryness	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Nasal inflammation	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Oropharyngeal pain	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Pulmonary embolism	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Respiratory failure	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Rhinitis allergic	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Sinus disorder	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Gastrointestinal disorders	57 (80.3) [155.4]	25 (37.9) [44.3]	82 (59.9) [88.1]
Abdominal distension	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Abdominal pain	6 (8.5) [4.8]	5 (7.6) [6.4]	11 (8.0) [5.4]
Abdominal pain upper	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Anal haemorrhage	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Angular cheilitis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Aphthous ulcer	2 (2.8) [1.5]	2 (3.0) [2.4]	4 (2.9) [1.9]
Cheilitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Constipation	8 (11.3) [6.6]	6 (9.1) [7.6]	14 (10.2) [7.0]
Dental caries	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Dental discomfort	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Diarrhoea	32 (45.1) [40.7]	10 (15.2) [13.4]	42 (30.7) [27.4]
Diarrhoea haemorrhagic	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Dry mouth	5 (7.0) [4.1]	3 (4.5) [3.7]	8 (5.8) [3.9]
Dyspepsia	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Eructation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Flatulence	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Food poisoning	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Gastrointestinal disorder	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Gastrooesophageal reflux disease	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Gingival atrophy	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Gingival swelling	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Haematemesis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Haemorrhoidal haemorrhage	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Haemorrhoids	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Infrequent bowel movements	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Intussusception	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Large intestine polyp	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Lip swelling	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Mouth haemorrhage	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Mouth ulceration	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Nausea	18 (25.4) [16.6]	8 (12.1) [10.2]	26 (19.0) [13.9]
Rectal haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Rectal tenesmus	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Stomatitis	7 (9.9) [5.9]	3 (4.5) [3.7]	10 (7.3) [5.0]
Tooth impacted	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Toothache	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Vomiting	21 (29.6) [20.6]	8 (12.1) [10.6]	29 (21.2) [16.4]
Hepatobiliary disorders	4 (5.6) [3.1]	0	4 (2.9) [1.9]
Bile duct stenosis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Hyperbilirubinaemia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Hypertransaminasaemia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Liver injury	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Skin and subcutaneous tissue disorders	66 (93.0) [535.2]	50 (75.8) [195.3]	116 (84.7) [305.8]
Acne	5 (7.0) [4.0]	5 (7.6) [6.4]	10 (7.3) [4.9]
Alopecia	15 (21.1) [14.3]	5 (7.6) [6.3]	20 (14.6) [10.8]
Dermatitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Dermatitis acneiform	43 (60.6) [74.4]	23 (34.8) [39.4]	66 (48.2) [56.8]
Dermatitis allergic	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Dermatitis atopic	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Dermatitis contact	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Drug eruption	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Dry skin	13 (18.3) [11.4]	7 (10.6) [9.1]	20 (14.6) [10.5]
Eczema	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Erythema	2 (2.8) [1.5]	2 (3.0) [2.4]	4 (2.9) [1.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Hair colour changes	3 (4.2) [2.3]	4 (6.1) [5.0]	7 (5.1) [3.3]
Hair growth abnormal	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Hair texture abnormal	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Hand dermatitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ingrowing nail	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Intertrigo	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nail disorder	2 (2.8) [1.5]	2 (3.0) [2.4]	4 (2.9) [1.9]
Nail fold inflammation	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Night sweats	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Onychoclasis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Onycholysis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Onychomalacia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Pain of skin	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Papule	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Photosensitivity reaction	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pruritus	7 (9.9) [5.6]	3 (4.5) [3.7]	10 (7.3) [4.9]
Rash	14 (19.7) [12.8]	14 (21.2) [20.1]	28 (20.4) [15.7]
Rash follicular	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Rash macular	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Rash maculo-papular	4 (5.6) [3.1]	0	4 (2.9) [1.9]
Rash papular	3 (4.2) [2.4]	5 (7.6) [6.4]	8 (5.8) [3.9]
Rosacea	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Seborrhoeic dermatitis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Sensitive skin	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Skin burning sensation	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Skin discharge	0	1 (1.5) [1.2]	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Skin discolouration	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Skin erosion	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Skin fissures	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Skin hypopigmentation	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Trichorrhexis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Xeroderma	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Musculoskeletal and connective tissue disorders	25 (35.2) [25.2]	17 (25.8) [23.7]	42 (30.7) [24.6]
Arthralgia	3 (4.2) [2.4]	1 (1.5) [1.2]	4 (2.9) [1.9]
Back pain	9 (12.7) [7.3]	2 (3.0) [2.4]	11 (8.0) [5.3]
Bone pain	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Bursitis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Greater trochanteric pain syndrome	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Intervertebral disc protrusion	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Joint swelling	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Muscle spasms	3 (4.2) [2.3]	2 (3.0) [2.4]	5 (3.6) [2.3]
Muscle twitching	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Musculoskeletal chest pain	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Musculoskeletal stiffness	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Myalgia	5 (7.0) [4.1]	1 (1.5) [1.2]	6 (4.4) [2.9]
Neck pain	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Osteoporosis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Pain in extremity	5 (7.0) [3.9]	5 (7.6) [6.3]	10 (7.3) [4.9]
Periostitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tendonitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Tenosynovitis	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Renal and urinary disorders	6 (8.5) [4.8]	4 (6.1) [4.9]	10 (7.3) [4.9]
Calculus urinary	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Cystitis noninfective	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Dysuria	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Haematuria	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Haemoglobinuria	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nephrolithiasis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Renal colic	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Urinary hesitation	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Urinary incontinence	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Pregnancy, puerperium and perinatal conditions	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Abortion spontaneous	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Reproductive system and breast disorders	7 (9.9) [5.6]	5 (7.6) [6.4]	12 (8.8) [5.9]
Abnormal uterine bleeding	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Dysmenorrhoea	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Haematospermia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Heavy menstrual bleeding	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Menstrual disorder	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Menstruation irregular	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Ovarian cyst	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Scrotal swelling	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Varicocele	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Vulvovaginal dryness	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Congenital, familial and genetic disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Hydrocele	1 (1.4) [0.8]	0	1 (0.7) [0.5]
General disorders and administration site conditions	41 (57.7) [61.3]	14 (21.2) [20.0]	55 (40.1) [40.2]
Asthenia	3 (4.2) [2.4]	0	3 (2.2) [1.4]
Chest discomfort	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Chest pain	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Chills	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Drug withdrawal syndrome	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Face oedema	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Fatigue	17 (23.9) [16.0]	1 (1.5) [1.2]	18 (13.1) [9.5]
Generalised oedema	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Malaise	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Mucosal inflammation	1 (1.4) [0.8]	2 (3.0) [2.5]	3 (2.2) [1.4]
Mucosal toxicity	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Oedema	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Oedema peripheral	11 (15.5) [9.5]	7 (10.6) [9.1]	18 (13.1) [9.4]
Peripheral swelling	4 (5.6) [3.1]	2 (3.0) [2.4]	6 (4.4) [2.8]
Puncture site haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pyrexia	7 (9.9) [5.7]	1 (1.5) [1.2]	8 (5.8) [3.9]
Swelling face	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Xerosis	0	2 (3.0) [2.4]	2 (1.5) [0.9]
Investigations	47 (66.2) [86.6]	37 (56.1) [73.5]	84 (61.3) [80.3]
Alanine aminotransferase increased	12 (16.9) [10.2]	7 (10.6) [8.9]	19 (13.9) [9.7]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Alpha hydroxybutyrate dehydrogenase increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Amylase increased	3 (4.2) [2.3]	1 (1.5) [1.2]	4 (2.9) [1.9]
Aspartate aminotransferase increased	13 (18.3) [11.5]	6 (9.1) [7.5]	19 (13.9) [9.9]
Blood alkaline phosphatase increased	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Blood bilirubin unconjugated increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Blood creatine phosphokinase MB decreased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Blood creatine phosphokinase increased	35 (49.3) [47.2]	24 (36.4) [38.5]	59 (43.1) [43.2]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Blood creatinine increased	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Blood lactate dehydrogenase increased	2 (2.8) [1.6]	1 (1.5) [1.2]	3 (2.2) [1.4]
Blood pressure increased	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Blood urea increased	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Body temperature increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ejection fraction decreased	5 (7.0) [4.0]	6 (9.1) [7.7]	11 (8.0) [5.4]
Gamma-glutamyltransferase increased	3 (4.2) [2.3]	0	3 (2.2) [1.4]
International normalised ratio increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Intraocular pressure increased	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Lipase increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Lymphocyte count decreased	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Lymphocyte count increased	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Myoglobin blood increased	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Neutrophil count decreased	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Occult blood	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Platelet count increased	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Protein urine present	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Transaminases increased	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Urine analysis abnormal	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Weight decreased	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Weight increased	4 (5.6) [3.2]	3 (4.5) [3.7]	7 (5.1) [3.4]
Injury, poisoning and procedural complications	14 (19.7) [12.3]	4 (6.1) [4.8]	18 (13.1) [9.2]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Ankle fracture	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Contusion	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Craniofacial fracture	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Face injury	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Fall	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Fibula fracture	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Foot fracture	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Gingival injury	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Joint dislocation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Joint injury	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ligament sprain	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Limb injury	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Multiple injuries	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.2.2 Number of subjects with adverse events by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Post-traumatic neck syndrome	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Postoperative wound complication	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Radius fracture	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Rib fracture	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Skin abrasion	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Thermal burn	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Wound	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs, sorted on international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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3.1.2.2 Schwere UE (CTCAE Grad ≥ 3)

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Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Subjects with AE of CTCAE grade 3 or higher	33 (46.5) [34.7]	18 (27.3) [26.2]	51 (37.2) [31.1]
Infections and infestations	11 (15.5) [9.1]	4 (6.1) [4.9]	15 (10.9) [7.4]
Appendicitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
COVID-19	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Cellulitis	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Folliculitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Kidney infection	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Paronychia	4 (5.6) [3.1]	1 (1.5) [1.2]	5 (3.6) [2.4]
Pneumonia	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Pneumonia aspiration	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Rash pustular	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Sepsis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Urinary tract infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Neurofibrosarcoma	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neurofibrosarcoma recurrent	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tumour haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Blood and lymphatic system disorders	0	4 (6.1) [4.9]	4 (2.9) [1.9]
Anaemia	0	2 (3.0) [2.4]	2 (1.5) [0.9]
Thrombocytopenia	0	2 (3.0) [2.4]	2 (1.5) [0.9]
Metabolism and nutrition disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Hypermagnesaemia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Psychiatric disorders	2 (2.8) [1.5]	0	2 (1.5) [0.9]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Anxiety	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Insomnia	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nicotine dependence	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Psychiatric decompensation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Self-induced vomiting	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nervous system disorders	4 (5.6) [3.1]	1 (1.5) [1.2]	5 (3.6) [2.4]
Headache	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Paraparesis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Syncope	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Eye disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Ulcerative keratitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Vascular disorders	3 (4.2) [2.3]	1 (1.5) [1.2]	4 (2.9) [1.9]
Deep vein thrombosis	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Haematoma	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Hypertension	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Respiratory, thoracic and mediastinal disorders	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Dyspnoea	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Oropharyngeal pain	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pulmonary embolism	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Gastrointestinal disorders	2 (2.8) [1.5]	2 (3.0) [2.4]	4 (2.9) [1.9]
Abdominal pain	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Aphthous ulcer	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Stomatitis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Skin and subcutaneous tissue disorders	2 (2.8) [1.5]	2 (3.0) [2.4]	4 (2.9) [1.9]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Dermatitis acneiform	2 (2.8) [1.5]	1 (1.5) [1.2]	3 (2.2) [1.4]
Rash	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Musculoskeletal and connective tissue disorders	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Muscle spasms	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Muscle twitching	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Renal and urinary disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Nephrolithiasis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pregnancy, puerperium and perinatal conditions	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Abortion spontaneous	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Reproductive system and breast disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Final DCO PSC
Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Ovarian cyst	0	1 (1.5) [1.2]	1 (0.7) [0.5]
General disorders and administration site conditions	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Drug withdrawal syndrome	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Fatigue	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Puncture site haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pyrexia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Investigations	11 (15.5) [9.2]	5 (7.6) [6.2]	16 (11.7) [8.0]
Alanine aminotransferase increased	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Aspartate aminotransferase increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Blood creatine phosphokinase increased	6 (8.5) [4.9]	4 (6.1) [4.9]	10 (7.3) [4.9]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.2.4.2 Number of subjects with adverse events of CTCAE grade 3 or higher by system organ class and preferred term
(On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Ejection fraction decreased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Gamma-glutamyltransferase increased	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Lipase increased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Lymphocyte count decreased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Transaminases increased	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Weight decreased	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Injury, poisoning and procedural complications	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Joint dislocation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Radius fracture	0	1 (1.5) [1.2]	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs of CTCAE grade 3 or higher, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs of CTCAE grade 3 or higher are counted once for each system organ class/preferred term. Includes only AEs that are treatment emergent during the on-selumetinib period. AE Adverse event. CTCAE Common Terminology Criteria for Adverse Events (version 5.0). MedDRA version 27.1. On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period. On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off. Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subjects with no AE are censored to last dose + 30 days or data-cut off date.
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3.1.2.3 Schwerwiegende unerwünschte Ereignisse (SUE)

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Table 14.3.4.1.2 Number of subjects with serious adverse events, by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Subjects with any SAE	14 (19.7) [11.5]	10 (15.2) [12.6]	24 (17.5) [11.9]
Infections and infestations	4 (5.6) [3.1]	3 (4.5) [3.6]	7 (5.1) [3.3]
COVID-19	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Cellulitis	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Kidney infection	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pneumonia	1 (1.4) [0.8]	2 (3.0) [2.4]	3 (2.2) [1.4]
Pneumonia aspiration	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Sepsis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Skin infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Urinary tract infection	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (4.2) [2.3]	1 (1.5) [1.2]	4 (2.9) [1.9]
Clear cell renal cell carcinoma	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple SAEs are counted once for each system organ class/preferred term.
Includes only SAEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 27.1. SAE Serious adverse event.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with SAE/ total on-selumetinib person-years (=sum of all individual exposure durations until SAE start in the on-selumetinib period). Subject with no SAE are censored to last dose + 30 days or data-cut off date.
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Table 14.3.4.1.2 Number of subjects with serious adverse events, by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Neurofibrosarcoma	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neurofibrosarcoma recurrent	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Tumour haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Psychiatric disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Psychiatric decompensation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nervous system disorders	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Headache	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Paraparesis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Eye disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Vision blurred	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Vascular disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Haematoma	0	1 (1.5) [1.2]	1 (0.7) [0.5]

[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple SAEs are counted once for each system organ class/preferred term.
Includes only SAEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 27.1. SAE Serious adverse event.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with SAE/ total on-selumetinib person-years (=sum of all individual exposure durations until SAE start in the on-selumetinib period). Subject with no SAE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae227.sas
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Table 14.3.4.1.2 Number of subjects with serious adverse events, by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Respiratory, thoracic and mediastinal disorders	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Dyspnoea	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Pulmonary embolism	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Musculoskeletal and connective tissue disorders	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Back pain	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Musculoskeletal chest pain	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Renal and urinary disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Nephrolithiasis	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pregnancy, puerperium and perinatal conditions	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Abortion spontaneous	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple SAEs are counted once for each system organ class/preferred term.
Includes only SAEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 27.1. SAE Serious adverse event.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with SAE/ total on-selumetinib person-years (=sum of all individual exposure durations until SAE start in the on-selumetinib period). Subject with no SAE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae227.sas
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Table 14.3.4.1.2 Number of subjects with serious adverse events, by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Reproductive system and breast disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Scrotal swelling	1 (1.4) [0.8]	0	1 (0.7) [0.5]
General disorders and administration site conditions	0	2 (3.0) [2.4]	2 (1.5) [0.9]
Drug withdrawal syndrome	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Puncture site haemorrhage	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pyrexia	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Injury, poisoning and procedural complications	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Joint dislocation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Radius fracture	0	1 (1.5) [1.2]	1 (0.7) [0.5]

[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple SAEs are counted once for each system organ class/preferred term.
Includes only SAEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 27.1. SAE Serious adverse event.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with SAE/ total on-selumetinib person-years (=sum of all individual exposure durations until SAE start in the on-selumetinib period). Subject with no SAE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae227.sas
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3.1.2.4 Abbruch der Studienmedikation aufgrund von UE

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Table 14.3.5.1.2 Number of subjects with adverse events leading to discontinuation of study intervention, by system organ class and preferred term (On-selumetinib safety analysis set)

System organ class Preferred term	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)] Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Subjects with any AE leading to discontinuation of study intervention [b]	11 (15.5) [8.4]	2 (3.0) [2.4]	13 (9.5) [6.0]
Infections and infestations	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Cellulitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Pneumonia aspiration	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Neurofibrosarcoma	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Neurofibrosarcoma recurrent	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Psychiatric disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Psychiatric decompensation	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Eye disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs leading to discontinuation of study intervention, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs leading to discontinuation of study intervention are counted once for each system organ class/preferred term. [b] Action taken, Drug Permanently Discontinued. Includes only AEs that are treatment emergent during the on-selumetinib period.
Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subject with no AE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae211.sas
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Final DCO PSC
Table 14.3.5.1.2 Number of subjects with adverse events leading to discontinuation of study intervention, by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Ulcerative keratitis	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Respiratory, thoracic and mediastinal disorders	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Pulmonary embolism	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Gastrointestinal disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Nausea	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Skin and subcutaneous tissue disorders	3 (4.2) [2.3]	0	3 (2.2) [1.4]
Dermatitis acneiform	2 (2.8) [1.5]	0	2 (1.5) [0.9]
Nail disorder	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Reproductive system and breast disorders	1 (1.4) [0.8]	0	1 (0.7) [0.5]
Scrotal swelling	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs leading to discontinuation of study intervention, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs leading to discontinuation of study intervention are counted once for each system organ class/preferred term. [b] Action taken, Drug Permanently Discontinued.
Includes only AEs that are treatment emergent during the on-selumetinib period.
Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subject with no AE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae211.sas
Executed: 2025-06-24T172549

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Table 14.3.5.1.2 Number of subjects with adverse events leading to discontinuation of study intervention, by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Injury, poisoning and procedural complications	1 (1.4) [0.8]	1 (1.5) [1.2]	2 (1.5) [0.9]
Postoperative wound complication	0	1 (1.5) [1.2]	1 (0.7) [0.5]
Wound	1 (1.4) [0.8]	0	1 (0.7) [0.5]

[a] Number (%) of subjects with AEs leading to discontinuation of study intervention, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple AEs leading to discontinuation of study intervention are counted once for each system organ class/preferred term. [b] Action taken, Drug Permanently Discontinued.
Includes only AEs that are treatment emergent during the on-selumetinib period.
Percentages are based on the total numbers of subjects in the treatment group (N). AE Adverse event. MedDRA version 27.1.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with AE/ total on-selumetinib person-years (=sum of all individual exposure durations until AE start in the on-selumetinib period). Subject with no AE are censored to last dose + 30 days or data-cut off date.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ae211.sas
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4 Rücklaufquoten

4.1 PAINS-pNF – chronischer Schmerz

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Baseline	Expected n	71	74
	0	0	0
	1	0	0
	2	6 (8.5)	8 (10.8)
	3	23 (32.4)	33 (44.6)
	4	42 (59.2)	33 (44.6)
Cycle 1	Expected n	71	74
	0	0	0
	1	0	0
	2	1 (1.4)	0
	3	0	0
	4	70 (98.6)	74 (100)
Cycle 2	Expected n	70	74
	0	0	0
	1	1 (1.4)	0

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 2	2	0	0
	3	0	0
	4	69 (98.6)	74 (100)
Cycle 3	Expected n	69	74
	0	0	0
	1	1 (1.4)	0
	2	1 (1.4)	0
	3	3 (4.3)	4 (5.4)
	4	64 (92.8)	70 (94.6)
Cycle 4	Expected n	66	74
	0	0	2 (2.7)
	1	0	0
	2	0	1 (1.4)
	3	1 (1.5)	1 (1.4)
	4	65 (98.5)	70 (94.6)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 5	Expected n	65	71
	0	0	0
	1	0	1 (1.4)
	2	0	0
	3	4 (6.2)	2 (2.8)
	4	61 (93.8)	68 (95.8)
Cycle 6	Expected n	65	70
	0	1 (1.5)	0
	1	0	1 (1.4)
	2	0	0
	3	5 (7.7)	0
	4	59 (90.8)	69 (98.6)
Cycle 7	Expected n	65	70
	0	0	0
	1	2 (3.1)	0

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 7	2	2 (3.1)	1 (1.4)
	3	3 (4.6)	1 (1.4)
	4	58 (89.2)	68 (97.1)
Cycle 8	Expected n	65	70
	0	0	0
	1	2 (3.1)	0
	2	1 (1.5)	1 (1.4)
	3	5 (7.7)	3 (4.3)
	4	57 (87.7)	66 (94.3)
Cycle 9	Expected n	64	69
	0	0	1 (1.4)
	1	0	0
	2	2 (3.1)	0
	3	3 (4.7)	1 (1.4)
	4	59 (92.2)	67 (97.1)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 10	Expected n	63	69
	0	0	0
	1	1 (1.6)	0
	2	0	2 (2.9)
	3	3 (4.8)	2 (2.9)
	4	59 (93.7)	65 (94.2)
Cycle 11	Expected n	62	67
	0	0	1 (1.5)
	1	0	0
	2	4 (6.5)	0
	3	3 (4.8)	1 (1.5)
	4	55 (88.7)	65 (97.0)
Cycle 12	Expected n	62	67
	0	1 (1.6)	0
	1	2 (3.2)	0

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 12	2	0	2 (3.0)
	3	4 (6.5)	0
	4	55 (88.7)	65 (97.0)
Cycle 13	Expected n	59	65
	0	0	2 (3.1)
	1	0	2 (3.1)
	2	0	0
	3	5 (8.5)	2 (3.1)
	4	54 (91.5)	59 (90.8)
Cycle 14	Expected n	59	64
	0	0	2 (3.1)
	1	0	0
	2	4 (6.8)	2 (3.1)
	3	3 (5.1)	0
	4	52 (88.1)	60 (93.8)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 15	Expected n	58	63
	0	0	2 (3.2)
	1	2 (3.4)	1 (1.6)
	2	2 (3.4)	0
	3	4 (6.9)	0
	4	50 (86.2)	60 (95.2)
Cycle 16	Expected n	57	63
	0	0	1 (1.6)
	1	1 (1.8)	1 (1.6)
	2	2 (3.5)	0
	3	3 (5.3)	2 (3.2)
	4	51 (89.5)	59 (93.7)
Cycle 17	Expected n	55	63
	0	1 (1.8)	3 (4.8)
	1	1 (1.8)	1 (1.6)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 17	2	2 (3.6)	0
	3	3 (5.5)	1 (1.6)
	4	48 (87.3)	58 (92.1)
Cycle 18	Expected n	55	62
	0	1 (1.8)	2 (3.2)
	1	1 (1.8)	1 (1.6)
	2	2 (3.6)	0
	3	2 (3.6)	3 (4.8)
	4	49 (89.1)	56 (90.3)
Cycle 19	Expected n	54	61
	0	2 (3.7)	2 (3.3)
	1	1 (1.9)	0
	2	2 (3.7)	4 (6.6)
	3	2 (3.7)	1 (1.6)
	4	47 (87.0)	54 (88.5)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 20	Expected n	54	60
	0	3 (5.6)	2 (3.3)
	1	0	0
	2	1 (1.9)	1 (1.7)
	3	3 (5.6)	2 (3.3)
	4	47 (87.0)	55 (91.7)
Cycle 21	Expected n	52	59
	0	3 (5.8)	4 (6.8)
	1	0	0
	2	2 (3.8)	1 (1.7)
	3	3 (5.8)	0
	4	44 (84.6)	54 (91.5)
Cycle 22	Expected n	52	58
	0	4 (7.7)	2 (3.4)
	1	1 (1.9)	1 (1.7)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 22	2	1 (1.9)	0
	3	2 (3.8)	1 (1.7)
	4	44 (84.6)	54 (93.1)
Cycle 23	Expected n	52	58
	0	1 (1.9)	2 (3.4)
	1	0	2 (3.4)
	2	5 (9.6)	1 (1.7)
	3	4 (7.7)	4 (6.9)
	4	42 (80.8)	49 (84.5)
Cycle 24	Expected n	51	57
	0	2 (3.9)	2 (3.5)
	1	0	0
	2	3 (5.9)	3 (5.3)
	3	4 (7.8)	4 (7.0)
	4	42 (82.4)	48 (84.2)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 25	Expected n	50	56
	0	4 (8.0)	8 (14.3)
	1	3 (6.0)	2 (3.6)
	2	1 (2.0)	2 (3.6)
	3	4 (8.0)	2 (3.6)
	4	38 (76.0)	42 (75.0)
Cycle 26	Expected n	46	47
	0	4 (8.7)	4 (8.5)
	1	3 (6.5)	1 (2.1)
	2	5 (10.9)	1 (2.1)
	3	1 (2.2)	2 (4.3)
	4	33 (71.7)	39 (83.0)
Cycle 27	Expected n	38	44
	0	2 (5.3)	4 (9.1)
	1	2 (5.3)	1 (2.3)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 27	2	4 (10.5)	1 (2.3)
	3	1 (2.6)	1 (2.3)
	4	29 (76.3)	37 (84.1)
Cycle 28	Expected n	35	39
	0	2 (5.7)	4 (10.3)
	1	2 (5.7)	0
	2	3 (8.6)	1 (2.6)
	3	3 (8.6)	0
	4	25 (71.4)	34 (87.2)
Cycle 29	Expected n	31	37
	0	2 (6.5)	2 (5.4)
	1	1 (3.2)	4 (10.8)
	2	1 (3.2)	1 (2.7)
	3	2 (6.5)	0
	4	25 (80.6)	30 (81.1)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 30	Expected n	28	33
	0	0	3 (9.1)
	1	1 (3.6)	2 (6.1)
	2	4 (14.3)	2 (6.1)
	3	3 (10.7)	1 (3.0)
	4	20 (71.4)	25 (75.8)
Cycle 31	Expected n	23	26
	0	1 (4.3)	1 (3.8)
	1	3 (13.0)	2 (7.7)
	2	3 (13.0)	1 (3.8)
	3	1 (4.3)	2 (7.7)
	4	15 (65.2)	20 (76.9)
Cycle 32	Expected n	17	21
	0	2 (11.8)	0
	1	2 (11.8)	1 (4.8)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 32	2	1 (5.9)	3 (14.3)
	3	1 (5.9)	1 (4.8)
	4	11 (64.7)	16 (76.2)
Cycle 33	Expected n	12	16
	0	0	1 (6.3)
	1	3 (25.0)	3 (18.8)
	2	2 (16.7)	1 (6.3)
	3	1 (8.3)	0
	4	6 (50.0)	11 (68.8)
Cycle 34	Expected n	9	10
	0	2 (22.2)	0
	1	0	1 (10.0)
	2	0	0
	3	1 (11.1)	0
	4	6 (66.7)	9 (90.0)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 35	Expected n	8	9
	0	1 (12.5)	0
	1	0	0
	2	0	0
	3	1 (12.5)	1 (11.1)
	4	6 (75.0)	8 (88.9)
Cycle 36	Expected n	7	9
	0	1 (14.3)	0
	1	0	0
	2	0	0
	3	0	0
	4	6 (85.7)	9 (100)
Cycle 37	Expected n	6	9
	0	0	0
	1	0	0

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 37	2	0	0
	3	1 (16.7)	0
	4	5 (83.3)	9 (100)
Cycle 38	Expected n	6	9
	0	0	0
	1	0	0
	2	1 (16.7)	0
	3	0	0
	4	5 (83.3)	9 (100)
Cycle 39	Expected n	5	7
	0	0	0
	1	1 (20.0)	0
	2	0	0
	3	0	1 (14.3)
	4	4 (80.0)	6 (85.7)

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

Study Code: D134BC00001 Phase III Page 17 of 18
Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 40	Expected n	3	7
	0	0	0
	1	0	2 (28.6)
	2	0	0
	3	1 (33.3)	1 (14.3)
	4	2 (66.7)	4 (57.1)
Cycle 41	Expected n	2	4
	0	0	1 (25.0)
	1	0	0
	2	0	0
	3	0	1 (25.0)
	4	2 (100)	2 (50.0)
Cycle 42	Expected n	2	2
	0	0	0
	1	0	0

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

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Final DCO PSC
Table 14.1.7.2 Distribution of eDiary entries for PAINS-pNF chronic target PN pain (Full analysis set)

		Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=74)
Timepoint	Number of non-overlapping 7-day periods with at least 4 daily pain scores	Number of subjects with daily diary entries n (%)	Number of subjects with daily diary entries n (%)
Cycle 42	2	1 (50.0)	0
	3	0	2 (100)
	4	1 (50.0)	0
Cycle 43	Expected n	1	2
	0	1 (100)	2 (100)
	1	0	0
	2	0	0
	3	0	0
	4	0	0

Percentages calculated among subjects with expected eDiary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN). Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds206.sas
Executed: 2025-06-24T172638

4.2 PAINS-pNF – Schmerzspitze

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Final DCO PSC
Table 14.1.7.4 Distribution of eDiary entries for PAINS-pNF spike target PN pain (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1542 (77.6)	2072	1532 (73.9)
Cycle 1	1942	1922 (99.0)	2072	2036 (98.3)
Cycle 2	1881	1841 (97.9)	2070	2023 (97.7)
Cycle 3	1835	1795 (97.8)	2044	1986 (97.2)
Cycle 4	1820	1748 (96.0)	2005	1955 (97.5)
Cycle 5	1820	1712 (94.1)	1960	1908 (97.3)
Cycle 6	1820	1660 (91.2)	1954	1892 (96.8)
Cycle 7	1809	1661 (91.8)	1932	1886 (97.6)
Cycle 8	1776	1651 (93.0)	1925	1861 (96.7)
Cycle 9	1712	1637 (95.6)	1904	1857 (97.5)
Cycle 10	1706	1617 (94.8)	1879	1840 (97.9)
Cycle 11	1659	1576 (95.0)	1870	1790 (95.7)
Cycle 12	1624	1551 (95.5)	1848	1782 (96.4)
Cycle 13	1596	1491 (93.4)	1784	1659 (93.0)
Cycle 14	1577	1468 (93.1)	1764	1639 (92.9)
Cycle 15	1566	1434 (91.6)	1738	1614 (92.9)
Cycle 16	1540	1442 (93.6)	1736	1633 (94.1)

[a] A diary entry is expected while on treatment. [b] A diary entry is considered completed if a daily spike target PAINS-pNF pain score was recorded. eDiary compliance is number of completed daily diary entries over the number of expected daily diary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN).
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds208.sas
Executed: 2025-06-24T172641

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Final DCO PSC
Table 14.1.7.4 Distribution of eDiary entries for PAINS-pNF spike target PN pain (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Cycle 17	1540	1360 (88.3)	1718	1576 (91.7)
Cycle 18	1531	1367 (89.3)	1694	1562 (92.2)
Cycle 19	1495	1333 (89.2)	1680	1523 (90.7)
Cycle 20	1478	1317 (89.1)	1666	1514 (90.9)
Cycle 21	1456	1257 (86.3)	1650	1465 (88.8)
Cycle 22	1443	1228 (85.1)	1604	1460 (91.0)
Cycle 23	1428	1257 (88.0)	1596	1411 (88.4)
Cycle 24	1421	1217 (85.6)	1589	1411 (88.8)
Cycle 25	1313	1120 (85.3)	1378	1215 (88.2)
Cycle 26	1129	978 (86.6)	1260	1109 (88.0)
Cycle 27	1023	869 (84.9)	1142	1019 (89.2)
Cycle 28	944	797 (84.4)	1067	933 (87.4)
Cycle 29	822	722 (87.8)	994	838 (84.3)
Cycle 30	730	653 (89.5)	821	728 (88.7)
Cycle 31	549	475 (86.5)	675	608 (90.1)
Cycle 32	415	346 (83.4)	537	501 (93.3)
Cycle 33	287	230 (80.1)	345	328 (95.1)

[a] A diary entry is expected while on treatment. [b] A diary entry is considered completed if a daily spike target PAINS-pNF pain score was recorded. eDiary compliance is number of completed daily diary entries over the number of expected daily diary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN).
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds208.sas
Executed: 2025-06-24T172641

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Final DCO PSC
Table 14.1.7.4 Distribution of eDiary entries for PAINS-pNF spike target PN pain (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Cycle 34	240	193 (80.4)	256	248 (96.9)
Cycle 35	217	182 (83.9)	252	237 (94.0)
Cycle 36	172	163 (94.8)	252	242 (96.0)
Cycle 37	168	157 (93.5)	252	248 (98.4)
Cycle 38	154	150 (97.4)	249	246 (98.8)
Cycle 39	117	116 (99.1)	196	188 (95.9)
Cycle 40	76	75 (98.7)	163	143 (87.7)
Cycle 41	56	56 (100)	96	74 (77.1)
Cycle 42	39	39 (100)	56	48 (85.7)
Cycle 43	6	0	14	0

[a] A diary entry is expected while on treatment. [b] A diary entry is considered completed if a daily spike target PAINS-pNF pain score was recorded. eDiary compliance is number of completed daily diary entries over the number of expected daily diary entries. N Number of subjects in treatment group. PAINS-pNF Pain Intensity Scale for Plexiform Neurofibroma (PN).
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds208.sas
Executed: 2025-06-24T172641

4.3 PN-Schmerzmedikation für chronische Schmerzen basierend auf dem elektronischen Tagebuch

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Final DCO PSC
Table 14.1.7.6 Distribution of eDiary entries for PN pain medication (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Baseline	1988	1498 (75.4)	2072	1449 (69.9)
Cycle 1	1942	1869 (96.2)	2072	1932 (93.2)
Cycle 2	1881	1778 (94.5)	2070	1931 (93.3)
Cycle 3	1835	1733 (94.4)	2044	1871 (91.5)
Cycle 4	1820	1682 (92.4)	2005	1877 (93.6)
Cycle 5	1820	1664 (91.4)	1960	1828 (93.3)
Cycle 6	1820	1623 (89.2)	1954	1803 (92.3)
Cycle 7	1809	1619 (89.5)	1932	1773 (91.8)
Cycle 8	1776	1597 (89.9)	1925	1747 (90.8)
Cycle 9	1712	1549 (90.5)	1904	1747 (91.8)
Cycle 10	1706	1526 (89.4)	1879	1747 (93.0)
Cycle 11	1659	1483 (89.4)	1870	1704 (91.1)
Cycle 12	1624	1444 (88.9)	1848	1680 (90.9)
Cycle 13	1596	1387 (86.9)	1784	1581 (88.6)
Cycle 14	1577	1384 (87.8)	1764	1552 (88.0)
Cycle 15	1566	1371 (87.5)	1738	1543 (88.8)
Cycle 16	1540	1369 (88.9)	1736	1525 (87.8)

[a] A diary entry is expected while on treatment. [b] A diary entry is considered completed if question "Did you take any medication for your tumour pain from the time you went to bed last night until now (including overnight)?" was answered and the items after it are answered if applicable. eDiary compliance is number of completed daily diary entries over the number of expected daily diary entries. N Number of subjects in treatment group.Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds209.sas
Executed: 2025-06-24T172643

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Final DCO PSC
Table 14.1.7.6 Distribution of eDiary entries for PN pain medication (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Cycle 17	1540	1328 (86.2)	1718	1494 (87.0)
Cycle 18	1531	1333 (87.1)	1694	1458 (86.1)
Cycle 19	1495	1305 (87.3)	1680	1422 (84.6)
Cycle 20	1478	1286 (87.0)	1666	1431 (85.9)
Cycle 21	1456	1225 (84.1)	1650	1386 (84.0)
Cycle 22	1443	1210 (83.9)	1604	1371 (85.5)
Cycle 23	1428	1219 (85.4)	1596	1357 (85.0)
Cycle 24	1421	1182 (83.2)	1589	1357 (85.4)
Cycle 25	1313	1090 (83.0)	1378	1158 (84.0)
Cycle 26	1129	929 (82.3)	1260	1053 (83.6)
Cycle 27	1023	851 (83.2)	1142	959 (84.0)
Cycle 28	944	774 (82.0)	1067	886 (83.0)
Cycle 29	822	714 (86.9)	994	821 (82.6)
Cycle 30	730	650 (89.0)	821	696 (84.8)
Cycle 31	549	472 (86.0)	675	598 (88.6)
Cycle 32	415	346 (83.4)	537	494 (92.0)
Cycle 33	287	229 (79.8)	345	317 (91.9)

[a] A diary entry is expected while on treatment. [b] A diary entry is considered completed if question "Did you take any medication for your tumour pain from the time you went to bed last night until now (including overnight)?" was answered and the items after it are answered if applicable. eDiary compliance is number of completed daily diary entries over the number of expected daily diary entries. N Number of subjects in treatment group.Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds209.sas
Executed: 2025-06-24T172643

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Final DCO PSC
Table 14.1.7.6 Distribution of eDiary entries for PN pain medication (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)		Placebo / Selumetinib 25 mg/m2 BID (N=74)	
Timepoint	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)	Number of expected daily diary entries [a]	Number of completed daily diary entries and eDiary compliance [b] (%)
Cycle 34	240	192 (80.0)	256	247 (96.5)
Cycle 35	217	177 (81.6)	252	234 (92.9)
Cycle 36	172	156 (90.7)	252	241 (95.6)
Cycle 37	168	148 (88.1)	252	244 (96.8)
Cycle 38	154	147 (95.5)	249	241 (96.8)
Cycle 39	117	115 (98.3)	196	186 (94.9)
Cycle 40	76	75 (98.7)	163	143 (87.7)
Cycle 41	56	56 (100)	96	72 (75.0)
Cycle 42	39	39 (100)	56	47 (83.9)
Cycle 43	6	0	14	0

[a] A diary entry is expected while on treatment. [b] A diary entry is considered completed if question "Did you take any medication for your tumour pain from the time you went to bed last night until now (including overnight)?" was answered and the items after it are answered if applicable. eDiary compliance is number of completed daily diary entries over the number of expected daily diary entries. N Number of subjects in treatment group.Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds209.sas
Executed: 2025-06-24T172643

4.4 PlexiQoL

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Final DCO PSC
Table 14.1.7.7 Instrument completion rate for PlexiQoL (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)				Placebo / Selumetinib 25 mg/m2 BID (N=74)			
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	71	70 (98.6)	70 (98.6)	71 (100)	74	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	67 (94.4)	67 (94.4)	67 (94.4)	74	74 (100)	74 (100)	74 (100)
Cycle 4, Day 28	65	65 (100)	65 (100)	65 (100)	73	69 (94.5)	69 (94.5)	69 (94.5)
Cycle 8, Day 28	65	61 (93.8)	61 (93.8)	61 (93.8)	69	67 (97.1)	67 (97.1)	67 (97.1)
Cycle 12, Day 28	60	61 (101.7)	61 (101.7)	61 (101.7)	67	64 (95.5)	64 (95.5)	64 (95.5)
Cycle 16, Day 28	56	54 (96.4)	54 (96.4)	54 (96.4)	63	63 (100)	63 (100)	63 (100)
Cycle 20, Day 28	54	54 (100)	54 (100)	54 (100)	60	60 (100)	60 (100)	60 (100)
Cycle 24, Day 28	51	44 (86.3)	44 (86.3)	44 (86.3)	57	51 (89.5)	51 (89.5)	51 (89.5)
Cycle 30, Day 28	35	17 (48.6)	17 (48.6)	17 (48.6)	39	26 (66.7)	26 (66.7)	26 (66.7)
Cycle 36, Day 28	9	6 (66.7)	6 (66.7)	6 (66.7)	11	7 (63.6)	7 (63.6)	7 (63.6)
Cycle 42, Day 28	3	1 (33.3)	1 (33.3)	1 (33.3)	7	2 (28.6)	2 (28.6)	2 (28.6)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100% when a subject continues to complete after discontinuation.
n Number of subjects per category. N Number of subjects in treatment group.
PlexiQoL Plexiform Neurofibroma Quality of Life scale. PRO Patient-reported outcome.
Full analysis set - subjects randomised to study intervention. If >3 items are missing, score is not derived.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds211.sas
Executed: 2025-06-24T172646

4.5 PII-pNF

Study Code: D134BC00001 Phase III Page 1 of 1
Final DCO PSC
Table 14.1.7.8 Instrument completion rate for PII-pNF (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)			Placebo / Selumetinib 25 mg/m2 BID (N=74)		
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)
Baseline	71	47 (66.2)	70 (98.6)	74	50 (67.6)	72 (97.3)
Cycle 1, Day 28	71	47 (66.2)	70 (98.6)	74	54 (73.0)	74 (100)
Cycle 2, Day 28	67	45 (67.2)	66 (98.5)	74	55 (74.3)	74 (100)
Cycle 4, Day 28	65	46 (70.8)	65 (100)	73	50 (68.5)	69 (94.5)
Cycle 6, Day 28	65	43 (66.2)	64 (98.5)	70	49 (70.0)	68 (97.1)
Cycle 8, Day 28	64	46 (71.9)	60 (93.8)	69	46 (66.7)	66 (95.7)
Cycle 10, Day 28	61	37 (60.7)	61 (100)	68	47 (69.1)	66 (97.1)
Cycle 12, Day 28	58	42 (72.4)	61 (105.2)	66	46 (69.7)	64 (97.0)
Cycle 16, Day 28	56	40 (71.4)	54 (96.4)	63	45 (71.4)	63 (100)
Cycle 20, Day 28	54	39 (72.2)	54 (100)	60	44 (73.3)	60 (100)
Cycle 24, Day 28	51	31 (60.8)	44 (86.3)	57	35 (61.4)	51 (89.5)
Cycle 30, Day 28	35	9 (25.7)	17 (48.6)	39	20 (51.3)	26 (66.7)
Cycle 36, Day 28	9	3 (33.3)	6 (66.7)	11	6 (54.5)	7 (63.6)
Cycle 42, Day 28	3	1 (33.3)	1 (33.3)	7	1 (14.3)	2 (28.6)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100% when a subject continues to complete after discontinuation.
n Number of subjects per category. N Number of subjects in treatment group.
PII-pNF Pain interference index - plexiform neurofibroma. PRO Patient-reported outcome.Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds213.sas
Executed: 2025-06-24T172647

4.6 PROMIS

Study Code: D134BC00001 Phase III Page 1 of 1
Final DCO PSC
Table 14.1.7.9 Instrument completion rate for PROMIS (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)			Placebo / Selumetinib 25 mg/m2 BID (N=74)		
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	At least one question completed [a] n (%)
Baseline	71	70 (98.6)	70 (98.6)	74	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	67 (94.4)	67 (94.4)	74	74 (100)	74 (100)
Cycle 4, Day 28	65	65 (100)	65 (100)	73	69 (94.5)	69 (94.5)
Cycle 8, Day 28	65	61 (93.8)	61 (93.8)	69	67 (97.1)	67 (97.1)
Cycle 12, Day 28	60	61 (101.7)	61 (101.7)	67	64 (95.5)	64 (95.5)
Cycle 16, Day 28	56	54 (96.4)	54 (96.4)	63	63 (100)	63 (100)
Cycle 20, Day 28	54	54 (100)	54 (100)	60	60 (100)	60 (100)
Cycle 24, Day 28	51	44 (86.3)	44 (86.3)	57	51 (89.5)	51 (89.5)
Cycle 30, Day 28	35	17 (48.6)	17 (48.6)	39	26 (66.7)	26 (66.7)
Cycle 36, Day 28	9	6 (66.7)	6 (66.7)	11	7 (63.6)	7 (63.6)
Cycle 42, Day 28	3	1 (33.3)	1 (33.3)	7	2 (28.6)	2 (28.6)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100% when a subject continues to complete after discontinuation.
n Number of subjects per category. N Number of subjects in treatment group.
PRO Patient-reported outcome. PROMIS Patient-Reported Outcomes Measurement Information System.
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds215.sas
Executed: 2025-06-24T172649

4.7 PedsQL NF1

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Final DCO PSC
Table 14.1.7.10 Instrument completion rate for PedsQL NF1 module (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)				Placebo / Selumetinib 25 mg/m2 BID (N=74)			
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	71	71 (100)	71 (100)	71 (100)	74	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	67 (94.4)	67 (94.4)	67 (94.4)	74	74 (100)	74 (100)	74 (100)
Cycle 4, Day 28	65	65 (100)	65 (100)	65 (100)	73	69 (94.5)	69 (94.5)	69 (94.5)
Cycle 8, Day 28	65	61 (93.8)	61 (93.8)	61 (93.8)	69	67 (97.1)	67 (97.1)	67 (97.1)
Cycle 12, Day 28	60	61 (101.7)	61 (101.7)	61 (101.7)	67	64 (95.5)	64 (95.5)	64 (95.5)
Cycle 16, Day 28	56	54 (96.4)	54 (96.4)	54 (96.4)	63	63 (100)	63 (100)	63 (100)
Cycle 20, Day 28	54	54 (100)	54 (100)	54 (100)	60	60 (100)	60 (100)	60 (100)
Cycle 24, Day 28	51	44 (86.3)	44 (86.3)	44 (86.3)	57	51 (89.5)	51 (89.5)	51 (89.5)
Cycle 30, Day 28	35	17 (48.6)	17 (48.6)	17 (48.6)	39	26 (66.7)	26 (66.7)	26 (66.7)
Cycle 36, Day 28	9	6 (66.7)	6 (66.7)	6 (66.7)	11	7 (63.6)	7 (63.6)	7 (63.6)
Cycle 42, Day 28	3	1 (33.3)	1 (33.3)	1 (33.3)	7	2 (28.6)	2 (28.6)	2 (28.6)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Adult version of PedsQL NF1 is used. Rate greater than 100% when a subject continues to complete after discontinuation. n Number of subjects per category. N Number of subjects in treatment group.
PedsQL NF1 Paediatric Quality of Life Inventory Neurofibromatosis type 1. PRO Patient-reported outcome.
Full analysis set - subjects randomised to study intervention. If >50% items are missing, score is not derived.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds217.sas
Executed: 2025-06-24T172650

4.8 EQ-5D-5L

Study Code: D134BC00001 Phase III Page 1 of 1
Final DCO PSC
Table 14.1.7.11 Instrument completion rate for EQ-5D-5L (Full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)				Placebo / Selumetinib 25 mg/m2 BID (N=74)			
Timepoint	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)	PRO assessment expected n	All questions completed [a] n (%)	Met minimum requirements for scoring [a] n (%)	At least one question completed [a] n (%)
Baseline	71	70 (98.6)	70 (98.6)	70 (98.6)	74	72 (97.3)	72 (97.3)	72 (97.3)
Cycle 2, Day 28	71	67 (94.4)	67 (94.4)	67 (94.4)	74	74 (100)	74 (100)	74 (100)
Cycle 4, Day 28	65	65 (100)	65 (100)	65 (100)	73	69 (94.5)	69 (94.5)	69 (94.5)
Cycle 8, Day 28	65	61 (93.8)	61 (93.8)	61 (93.8)	69	67 (97.1)	67 (97.1)	67 (97.1)
Cycle 12, Day 28	60	61 (101.7)	61 (101.7)	61 (101.7)	67	64 (95.5)	64 (95.5)	64 (95.5)
Cycle 16, Day 28	56	54 (96.4)	54 (96.4)	54 (96.4)	63	63 (100)	63 (100)	63 (100)
Cycle 20, Day 28	54	54 (100)	54 (100)	54 (100)	60	59 (98.3)	59 (98.3)	59 (98.3)
Cycle 24, Day 28	51	44 (86.3)	44 (86.3)	44 (86.3)	57	51 (89.5)	51 (89.5)	51 (89.5)
Cycle 30, Day 28	35	17 (48.6)	17 (48.6)	17 (48.6)	39	26 (66.7)	26 (66.7)	26 (66.7)
Cycle 36, Day 28	9	6 (66.7)	6 (66.7)	6 (66.7)	11	7 (63.6)	7 (63.6)	7 (63.6)
Cycle 42, Day 28	3	1 (33.3)	1 (33.3)	1 (33.3)	7	2 (28.6)	2 (28.6)	2 (28.6)

[a] Completion rate is calculated among subjects with a PRO assessment expected. Subjects are expected to complete PROs while on treatment. Rate greater than 100% when a subject continues to complete after discontinuation.
EQ-5D-5L EuroQoL five dimensions. n Number of subjects per category. N Number of subjects in treatment group.PRO Patient-reported outcome.
Full analysis set - subjects randomised to study intervention.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds219.sas
Executed: 2025-06-24T172652

5 Disposition

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Final DCO PSC
Table 14.1.1.1 Subject disposition (Enrolled subjects)

	Number (%) of subjects		
	Selumetinib 25 mg/m2 BID	Placebo / Selumetinib 25 mg/m2 BID	Total
Subjects enrolled [a]			184
Subjects randomised [b]	71 (100)	74 (100)	145 (100)
Subjects who were not randomised			39
Screen failure			28
Pains-PNF score <3 strata closed			10
Withdrawal by subject			1
Subjects who received study intervention [b]	71 (100)	74 (100)	145 (100)
Subjects who did not receive study intervention [b]	0	0	0
Subjects who crossed over to selumetinib [c]	NA	66 (89.2)	66 (45.5)
Started selumetinib treatment prior to end of Cycle 12 visit [c]	NA	3 (4.1)	3 (2.1)
Started selumetinib treatment after end of Cycle 12 visit [c]	NA	63 (85.1)	63 (43.4)
Subjects completed study intervention at data cut-off date [c] [d]	45 (63.4)	51 (68.9)	96 (66.2)
Subjects moving to the continued access phase	45 (63.4)	51 (68.9)	96 (66.2)
Subjects not moving to the continued access phase	0	0	0
Subjects who discontinued study intervention [c]	26 (36.6)	23 (31.1)	49 (33.8)
Subject decision	8 (11.3)	15 (20.3)	23 (15.9)
Adverse event	12 (16.9)	7 (9.5)	19 (13.1)
Subjective disease progression	4 (5.6)	0	4 (2.8)

[a] Informed consent received.
[b] Percentages are calculated from the number of subjects who were randomised.
[c] Percentages are calculated from the number of subjects who received study intervention.
[d] Patients who were on-study intervention by the final data cut-off date regardless if they want to move to the continued access phase of the study or not, are considered as study intervention completer.
Reasons are sorted by decreasing frequency of the total column and then alphabetically.NA Not applicable.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds200.sas
Executed: 2025-06-24T172630

Study Code: D134BC00001 Phase III
Final DCO PSC
Table 14.1.1.1 Subject disposition (Enrolled subjects)

	Number (%) of subjects		
	Selumetinib 25 mg/m2 BID	Placebo / Selumetinib 25 mg/m2 BID	Total
Pregnancy	1 (1.4)	0	1 (0.7)
Subject lost to follow-up	1 (1.4)	0	1 (0.7)
Other	0	1 (1.4)	1 (0.7)
Subjects who discontinued study intervention prior to end of Cycle 12 visit [c]	13 (18.3)	9 (12.2)	22 (15.2)
Adverse event	7 (9.9)	5 (6.8)	12 (8.3)
Subject decision	4 (5.6)	4 (5.4)	8 (5.5)
Subject lost to follow-up	1 (1.4)	0	1 (0.7)
Subjective disease progression	1 (1.4)	0	1 (0.7)
Subjects completed study at data cut-off date [b]	45 (63.4)	51 (68.9)	96 (66.2)
Subjects who terminated study [b]	26 (36.6)	23 (31.1)	49 (33.8)
Adverse event	11 (15.5)	7 (9.5)	18 (12.4)
Withdrawal by subject	7 (9.9)	8 (10.8)	15 (10.3)
Other	1 (1.4)	7 (9.5)	8 (5.5)
Progressive disease	4 (5.6)	0	4 (2.8)
Lost to follow-up	1 (1.4)	1 (1.4)	2 (1.4)
Death	1 (1.4)	0	1 (0.7)
Pregnancy	1 (1.4)	0	1 (0.7)

[a] Informed consent received.
[b] Percentages are calculated from the number of subjects who were randomised.
[c] Percentages are calculated from the number of subjects who received study intervention.
[d] Patients who were on-study intervention by the final data cut-off date regardless if they want to move to the continued access phase of the study or not, are considered as study intervention completer.
Reasons are sorted by decreasing frequency of the total column and then alphabetically.NA Not applicable.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ds200.sas
Executed: 2025-06-24T172630

6 Dauer der Behandlung

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Final DCO PSC
Table 14.3.1.1.2 Duration of exposure, on-selumetinib period (On-selumetinib safety analysis set)

Characteristic	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Total exposure (days) [a]	n	71	66	137
	Mean	675.1	462.0	572.4
	SD	300.78	192.46	275.12
	Min	11	10	10
	Q1	515.0	344.0	372.0
	Median	749.0	475.5	566.0
	Q3	862.0	566.0	789.0
	Max	1182	844	1182
	Total treatment days	47932	30491	78423
Total exposure periods, n (%) [a]				
n	n (%)	71 (100)	66 (100)	137 (100)
< 12 months	n (%)	14 (19.7)	20 (30.3)	34 (24.8)
>= 12 - <= 24 months	n (%)	19 (26.8)	38 (57.6)	57 (41.6)
> 24 - <= 36 months	n (%)	35 (49.3)	8 (12.1)	43 (31.4)
> 36 months	n (%)	3 (4.2)	0	3 (2.2)

[a] Total exposure = last selumetinib dose date - first selumetinib dose date + 1. [b] Actual exposure = total selumetinib exposure - total duration of selumetinib dose interruptions. [c] Cycle is 28 days. [d] Relative dose intensity = 100% * d/D, where d is actual cumulative selumetinib dose up to last selumetinib dose date and D is intended cumulative selumetinib dose up to last selu dose date. [e] Compliance to IP is actual cumulative selumetinib dose relative to intended cumulative selumetinib dose adjusted for protocol-allowable dose reductions/interruptions up to and including last selumetinib dose date. Last dose date for on-selumetinib period is earliest of last dose of selumetinib, data cut-off or date of early discontinuation/death while taking selumetinib. For subjects randomised to placebo, only exposure after crossover is summarised. On-selumetinib period - from first dose of selumetinib until 30 days after last dose of selumetinib or up to day prior to start of subsequent therapy or data cut-off (whichever occurs first). IP Investigational product. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ex201.sas
Executed: 2025-06-24T172828

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Final DCO PSC
Table 14.3.1.1.2 Duration of exposure, on-selumetinib period (On-selumetinib safety analysis set)

Characteristic	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Actual exposure (days) [b]	n	71	66	137
	Mean	660.5	448.4	558.3
	SD	297.49	193.48	273.42
	Min	11	10	10
	Q1	496.0	344.0	357.0
	Median	735.0	457.0	554.0
	Q3	847.0	547.0	768.0
	Max	1156	833	1156
	Total treatment days	46894	29592	76485
Actual exposure periods, n (%) [b]				
n	n (%)	71 (100)	66 (100)	137 (100)
< 12 months	n (%)	15 (21.1)	21 (31.8)	36 (26.3)
>= 12 - <= 24 months	n (%)	20 (28.2)	39 (59.1)	59 (43.1)
> 24 - <= 36 months	n (%)	33 (46.5)	6 (9.1)	39 (28.5)
> 36 months	n (%)	3 (4.2)	0	3 (2.2)

[a] Total exposure = last selumetinib dose date - first selumetinib dose date + 1. [b] Actual exposure = total selumetinib exposure - total duration of selumetinib dose interruptions. [c] Cycle is 28 days. [d] Relative dose intensity = 100% * d/D, where d is actual cumulative selumetinib dose up to last selumetinib dose date and D is intended cumulative selumetinib dose up to last selu dose date. [e] Compliance to IP is actual cumulative selumetinib dose relative to intended cumulative selumetinib dose adjusted for protocol-allowable dose reductions/interruptions up to and including last selumetinib dose date. Last dose date for on-selumetinib period is earliest of last dose of selumetinib, data cut-off or date of early discontinuation/death while taking selumetinib. For subjects randomised to placebo, only exposure after crossover is summarised. On-selumetinib period - from first dose of selumetinib until 30 days after last dose of selumetinib or up to day prior to start of subsequent therapy or data cut-off (whichever occurs first). IP Investigational product. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ex201.sas
Executed: 2025-06-24T172828

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Final DCO PSC
Table 14.3.1.1.2 Duration of exposure, on-selumetinib period (On-selumetinib safety analysis set)

Characteristic	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Number of cycles [c]	n	71	66	137
	Mean	24.6	17.0	20.9
	SD	10.74	6.89	9.83
	Min	1	1	1
	Q1	19.0	13.0	14.0
	Median	27.0	17.0	21.0
	Q3	31.0	21.0	29.0
	Max	43	31	43
Relative dose intensity [d]	n	71	66	137
	Mean	91.4	92.7	92.0
	SD	12.75	13.82	13.24
	Min	54	34	34
	Q1	86.5	92.1	90.9
	Median	97.7	100.0	99.5
	Q3	100.0	100.0	100.0
	Max	103	100	103

[a] Total exposure = last selumetinib dose date - first selumetinib dose date + 1. [b] Actual exposure = total selumetinib exposure - total duration of selumetinib dose interruptions. [c] Cycle is 28 days. [d] Relative dose intensity = 100% * d/D, where d is actual cumulative selumetinib dose up to last selumetinib dose date and D is intended cumulative selumetinib dose up to last selu dose date. [e] Compliance to IP is actual cumulative selumetinib dose relative to intended cumulative selumetinib dose adjusted for protocol-allowable dose reductions/interruptions up to and including last selumetinib dose date. Last dose date for on-selumetinib period is earliest of last dose of selumetinib, data cut-off or date of early discontinuation/death while taking selumetinib. For subjects randomised to placebo, only exposure after crossover is summarised. On-selumetinib period - from first dose of selumetinib until 30 days after last dose of selumetinib or up to day prior to start of subsequent therapy or data cut-off (whichever occurs first). IP Investigational product. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
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Final DCO PSC
Table 14.3.1.1.2 Duration of exposure, on-selumetinib period (On-selumetinib safety analysis set)

Characteristic	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Compliance to IP (%) [e]	n	71	66	137
	Mean	98.6	99.2	98.9
	SD	3.68	3.87	3.77
	Min	78	70	70
	Q1	99.4	100.0	99.8
	Median	100.0	100.0	100.0
	Q3	100.0	100.0	100.0
	Max	101	100	101
Compliance to IP (%) [e]				
<80	n (%)	1 (1.4)	1 (1.5)	2 (1.5)
>=80 - <=100	n (%)	69 (97.2)	63 (95.5)	132 (96.4)
>100	n (%)	1 (1.4)	2 (3.0)	3 (2.2)

[a] Total exposure = last selumetinib dose date - first selumetinib dose date + 1. [b] Actual exposure = total selumetinib exposure - total duration of selumetinib dose interruptions. [c] Cycle is 28 days. [d] Relative dose intensity = 100% * d/D, where d is actual cumulative selumetinib dose up to last selumetinib dose date and D is intended cumulative selumetinib dose up to last selu dose date. [e] Compliance to IP is actual cumulative selumetinib dose relative to intended cumulative selumetinib dose adjusted for protocol-allowable dose reductions/interruptions up to and including last selumetinib dose date. Last dose date for on-selumetinib period is earliest of last dose of selumetinib, data cut-off or date of early discontinuation/death while taking selumetinib. For subjects randomised to placebo, only exposure after crossover is summarised. On-selumetinib period - from first dose of selumetinib until 30 days after last dose of selumetinib or up to day prior to start of subsequent therapy or data cut-off (whichever occurs first). IP Investigational product. Max Maximum. Min Minimum. n Number of subjects included in analysis. N Number of subjects in treatment group. Q1 1st quartile. Q3 3rd quartile. SD Standard deviation.
Program: /alxn/koselugo-nf1-d134bc00001/koselugo-nf1-d134bc00001-fapsc/Files/tables/production/programs/ex201.sas
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