Selumetinib (plexiform neurofibromas in adults with neurofibromatosis type 1)

Addendum to Project A25-147 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
NRS	numerical rating scale
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PlexiQoL	Plexiform Neurofibroma Quality of Life Scale
PII-pNF	Pain Interference Index for Plexiform Neurofibroma
PRO	patient-reported outcome
RCT	randomised controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 24 March 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-147 (Selumetinib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the analyses presented by the pharmaceutical company (hereinafter referred to as 'the company'), taking into account the information provided in the dossier:

- Return rates for the individual items of the Pain Interference Index for Plexiform Neurofibroma (PII-pNF) and the questionnaire on the 'Challenging Physical Activities' item of the PII-pNF
- Responder analyses on improvement at the end of the randomised study phase (Week 48)
- Responder analyses on the time to permanent improvement
- Outcome of volume change of the target lesion
- Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC)

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

1.1 Changes compared with Version 1.0

The present Version 1.1 of 13 April 2026 replaces Version 1.0 of the addendum of 10 April 2026. The following change is contained in Version 1.1 compared with Version 1.0:

- In Table 2, the classification of the added benefit derived at outcome level for the outcome spikes of pain (NRS – improvement at Week 48) was corrected from lesser benefit to added benefit.

The change has no impact on the conclusion of the benefit assessment.

2 Assessment

The KOMET randomised controlled trial (RCT) was used for benefit assessment of selumetinib for symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1. A detailed description of the study can be found in dossier assessment A25-147 [1].

The company dossier [2] contained time-to-event analyses for the included patient-reported outcomes (PROs), covering both the time to first improvement and the time to first deterioration of ≥15% of the scale range. In addition, analyses of the continuous data using a mixed-effects model with repeated measures (MMRM) were available. Dossier assessment A25-147 [1] stated that, in the therapeutic indication under consideration, it would be useful to present responder analyses (of improvement) for the PROs for the end of the randomised study phase (Week 48).

Within the commenting procedure, the company submitted, amongst other things, analyses on the improvement of 15% of the scale range at Week 48, and on the time to permanent improvement, for the PROs already considered in the dossier assessment. In addition, the company provided information on return rates for individual items in the PII-pNF (including the item 'Challenging Physical Activities').

As in dossier assessment A25-147, the following PROs were used to assess the added benefit:

- Chronic pain recorded using a numerical rating scale (NRS)
- Spikes of pain recorded using an NRS
- Pain interference using the PII-pNF
- Psychosocial morbidity recorded using the Plexiform Neurofibroma Quality of Life Scale (PlexiQoL)
- Health status recorded using the visual analogue scale (VAS) of the EQ-5D

The information and analyses subsequently submitted by the company during the commenting procedure [3] are assessed in detail below.

2.1 Notes on outcomes and analyses

Notes on outcomes

Pain interference (PII-pNF)

The PII-pNF uses 12 items to assess whether, and to what extent, pain caused by plexiform neurofibroma impairs daily functioning. The items are assessed on a 7-point Likert scale (0 = 'not at all' to 6 = 'completely'). For the item 'Challenging Physical Activities', there is also the response option 'does not apply'. A total score is calculated, with lower scores indicating

better daily functioning. The recall period is 7 days. The PII-pNF is considered a valid tool for recording pain interference in patients with neurofibromatosis type I and plexiform neurofibromas [4].

The results for the PII-pNF were not presented in dossier assessment A25-147 [1] as, according to the information in the company's dossier [2], fully completed questionnaires were missing for over 30% of patients at baseline in both treatment arms, meaning that the validity of the presented data remained unclear. In its comments, the company provided further details on the return rates for the individual items in the PII-pNF, including the item 'Challenging Physical Activities'. These figures show that, at baseline, 11 out of 12 items were answered by approximately 98% of patients. A lower return rate was observed only for the item 'Challenging Physical Activities' (already around 67% at baseline). The company stated that any missing data for this item was due to the 'does not apply' option having been ticked. The information in the company's dossier showed that the total PII-pNF score was calculated in each case as the mean of the completed items. This was appropriate.

The PII-pNF responder analyses submitted within the commenting procedure were used for the benefit assessment.

Pain recorded using the PGIS and PGIC

In the KOMET study, the outcome pain was recorded using several instruments. The PGIS and the PGIC were used in addition to the daily recording of chronic pain and spikes of pain, in each case using an NRS for a physician-identified target lesion (see A25-147 [1]). The PGIS consists of 2 items, each of which assesses chronic pain / spikes of pain relating to the target lesion on a Likert scale (4 levels ranging from 'no pain' to 'severe pain'). The recall period is 7 days. The PGIC is recorded in 2 versions (PGIC 1 and PGIC 2). For both versions, 2 items are used for recording changes in chronic pain / spikes of pain in relation to the plexiform neurofibroma. The questions in PGIC 1 relate to the period since the last visit. The questions in PGIC 2 relate to the period since starting the study medication. PGIC 1 and PGIC 2 are recorded using a 7-point Likert scale with response options ranging from 'very much improved' to 'very much worse'. As the PGIC questions relate specifically to a single plexiform neurofibroma, it was assumed that the PGIC also referred to the same lesion as the recordings of chronic pain and spikes of pain using the NRS and PGIS.

The PGIS and PGIC outcomes were not taken into account in the dossier assessment, as they were only recorded for individual visits within a cycle in the KOMET study. In contrast, chronic pain (NRS) and spikes of pain (NRS) were recorded daily (see A25-147 [1]). Furthermore, the PGIC and PGIS items recorded in the KOMET study represented the same construct already recorded by the NRS for chronic pain and spikes of pain, and therefore did not provide any

further information relevant to the benefit assessment. The results for the pain outcome, as assessed using the PGIC and PGIS, are presented in Appendix B.

Volume change of the target lesion

As already explained in detail in dossier assessment A25-147 [1], the operationalisations of the outcome volume change of the target lesion submitted by the company were assessed as not patient-relevant. Results of the responder analyses using a response threshold of ≥20% are presented in Appendix B.

Analyses of further outcomes

In its comments, the company presented responder analyses on the outcomes pain relief for chronic pain, a reduction in pain medication for chronic pain, physical functioning and health-related quality of life. The results for these outcomes are not presented. Detailed reasons for this can be found in dossier assessment A25-147 [1].

Analyses presented by the company

In its comments, as described in the dossier assessment, the company submitted responder analyses on the improvement of 15% of the scale range at Week 48, as well as additional time-to-event analyses of the time to permanent improvement.

The responder analyses of the improvement at Week 48 were used for the assessment. The time-to-event analyses of the time to permanent improvement are shown in Appendix A.

2.2 Risk of bias

The outcome-specific risk of bias of the results on the outcomes of the morbidity category was rated as high. The reason for this was that, as already described in dossier assessment A25-147, a varying proportion of patients in the intervention arm (18.3%) and the comparator arm (12.2%) discontinued the study medication prematurely before the end of the randomised treatment phase. The distribution of reasons for discontinuation differed between the treatment arms. The return rates for patient-reported outcomes fell to around 80% by Week 48 in both study arms. Overall, this resulted in a high risk of bias in the results for morbidity outcomes due to incomplete observations for potentially informative reasons.

2.3 Results

Table 1 shows the results of the comparison of selumetinib and placebo in adult patients with symptomatic, inoperable plexiform neurofibromas in neurofibromatosis type 1. The data from the dossier, as well as the subsequently submitted data from the company's comments, were supplemented using calculations conducted by the Institute where necessary.

Table 1: Results (morbidity, dichotomous) – RCT, direct comparison: selumetinib vs. placebo

Study Outcome category Outcome	selumetinib N	 Patients with event n (%)	placebo N	 Patients with event n (%)	selumetinib vs. placebo RR [95% CI][a]; p-value[b]
KOMET					
Morbidity					
Improvement at Week 48					
Chronic pain (NRS[c])	57	25 (43.9)	62	16 (25.8)	1.70 [1.02; 2.84]; 0.042
Spikes of pain (NRS[c])	58	39 (67.2)	64	25 (39.1)	1.72 [1.21; 2.45]; 0.002
Pain interference (PII-pNF[d])	57	27 (47.4)	59	18 (30.5)	1.55 [0.97; 2.49]; 0.067
Psychosocial morbidity (PlexiQoL[e])	57	17 (29.8)	59	19 (32.2)	0.93 [0.54; 1.60]; 0.828
Health status (EQ-5D VAS[f])	57	18 (31.6)	59	13 (22.0)	1.43 [0.78; 2.65]; 0.260

a. Institute's calculation.
b. Institute's calculation, unconditional exact test (CSZ method according to [5]).
c. A decrease by ≥1.5 points from baseline is considered a clinically relevant improvement (scale range: 1 to 10).
d. A decrease of ≥0.9 points from baseline is considered a clinically relevant improvement (scale range: 0 to 6).
e. A decrease by ≥2.7 points from baseline is considered a clinically relevant improvement (scale range: 1 to 18).
f. An increase by ≥15 points from baseline is considered a clinically relevant improvement (scale range: 0 to 100).

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; NRS: numerical rating scale; PII-pNF: Pain Interference Index for Plexiform Neurofibroma; PlexiQoL: Plexiform Neurofibroma Quality of Life Scale; RCT: randomised controlled trial; RR: relative risk; VAS: visual analogue scale

On the basis of the available information, at most hints, e.g. of an added benefit, can be determined for outcomes in the morbidity category.

Chronic pain (NRS)

For the outcome chronic pain (NRS) a statistically significant difference was found in favour of selumetinib in comparison with placebo. The extent of the effect was no more than marginal, however. There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

Spikes of pain (NRS)

For the outcome spikes of pain (NRS) a statistically significant difference was found in favour of selumetinib in comparison with placebo. There is a hint of an added benefit of selumetinib in comparison with placebo.

Pain interference (PII-pNF)

No statistically significant difference between the treatment arms was shown for the outcome pain interference (PII-pNF). There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

Psychosocial morbidity (PlexiQoL)

No statistically significant difference between the treatment arms was shown for the outcome psychosocial morbidity (PlexiQoL). There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome health status, recorded using the EQ-5D VAS. There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

2.4 Subgroups and other effect modifiers

The following potential effect modifiers were taken into account for this benefit assessment (see dossier assessment A25-147 [1]):

- Age (<30 years versus ≥30 years)
- Sex (male versus female)

The methods described in Section I 4.4 of dossier assessment A25-147 [1] were used for this purpose.

Based on the available subgroup results, no relevant effect modifications due to the characteristics age or sex were identified in accordance with the methodology described therein.

2.5 Probability and extent of added benefit

2.5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated based on the results presented in Table 1. Table 2 shows only the results assessed in this addendum for the outcomes chronic pain (NRS), spikes of pain (NRS), pain interference (PII-pNF), psychosocial morbidity (PlexiQoL) and health status (EQ-5D VAS).

Determination of the outcome category for the morbidity outcomes

For the morbidity outcomes below, it could not be inferred from the dossier whether they were serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Chronic pain (NRS) and spikes of pain (NRS)

For the outcomes chronic pain (NRS) and spikes of pain (NRS), insufficient information was available to allow a severity category classification of serious or severe. The outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Table 2: Extent of added benefit at outcome level: selumetinib vs. BSC

Outcome category **Outcome**	**selumetinib vs. placebo proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
Chronic pain (NRS – improvement at Week 48)	43.9% vs. 25.8% RR: 1.70 [1.02; 2.84] RR: 0.59 [0.35; 0.98][c]; p=0.042	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser benefit not proven / added benefit not proven[d]
Spikes of pain (NRS – improvement at Week 48)	67.2% vs. 39.1% RR: 1.72 [1.21; 2.45] RR: 0.58 [0.41; 0.83][c]; p=0.002 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: minor
Pain interference (PII-pNF – improvement at Week 48)	47.4% vs. 30.5% RR: 1.55 [0.97; 2.49]; p=0.067	Lesser benefit not proven / added benefit not proven
Psychosocial morbidity (PlexiQoL – improvement at Week 48)	29.8% vs. 32.2% RR: 0.93 [0.54; 1.60]; p=0.828	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS – improvement at Week 48)	31.6% vs. 22.0% RR: 1.43 [0.78; 2.65]; p=0.260	Lesser benefit not proven / added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

BSC: best supportive care; CI: confidence interval; CI_u: upper limit of the confidence interval; NRS: numerical rating scale; PII-pNF: Pain Interference Index for Plexiform Neurofibroma; PlexiQoL: Plexiform Neurofibroma Quality of Life Scale; RR: relative risk; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 3 summarises the results taken into account for the overall conclusion on the extent of the added benefit.

Table 3: Positive and negative effects from the assessment of selumetinib in comparison with BSC

Positive effects	**Negative effects**
Morbidity Non-serious/non-severe symptoms / late complications ▪ Spikes of pain (NRS): hint of an added benefit – extent: minor	–
–	Serious/severe side effects ▪ Severe AEs: hint of greater harm – extent: minor ▫ Infections and infestations (severe AEs): hint of greater harm – extent: minor ▫ Investigations (severe AEs): hint of greater harm – extent: major
–	Non-serious/non-severe side effects ▪ Specific AEs: ▫ Gastrointestinal disorders (AEs): hint of greater harm – extent: considerable ▫ Skin and subcutaneous tissue disorders (AEs): hint of greater harm – extent: considerable ▫ Oedema peripheral (AEs): hint of greater harm – extent: considerable
No suitable data were available for the outcome physical functioning. Outcomes on health-related quality of life were not recorded.	
AE: adverse event; BSC: best supportive care; NRS: numerical rating scale	

Overall, both positive and negative effects of selumetinib were shown in comparison with the ACT. In the morbidity outcome category there is a hint of an added benefit of minor extent. In contrast, in the side effects outcome category there are several hints of greater harm, including for the overall rate of severe adverse events (AEs) of minor extent, and for various specific severe AEs and non-serious/non-severe AEs of up to major extent.

In summary, for symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1, there is a hint of a minor added benefit of selumetinib versus the ACT, best supportive care.

2.6 Summary

The data subsequently submitted by the company in the commenting procedure altered the conclusion on the added benefit of selumetinib from dossier assessment A25-147: Overall, there is a hint of a minor added benefit.

The following Table 4 shows the result of the benefit assessment of selumetinib, taking into account dossier assessment A25-147 and this addendum.

Table 4: Selumetinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment of symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1	BSC[b]	Hint of a minor added benefit

a. Presented is the ACT specified by the G-BA.
b. BSC refers to the therapy that provides the patient with the best possible, individually optimised, supportive treatment to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Selumetinib (plexiforme Neurofibrome bei Neurofibromatose Typ 1, Erwachsene); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2026 [Accessed: 30.03.2026]. URL: https://doi.org/10.60584/A25-147.

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Appendix A Time-to-event analyses on the time to permanent improvement

The company defined a permanent improvement as the time to improvement without any subsequent deterioration. For the outcomes chronic pain (NRS), spikes of pain (NRS) and pain interference (PII-pNF), the company provided data on the proportion of patients with confirmed improvement (without subsequent deterioration), a one-off improvement at the end of the study, and a one-off improvement without a follow-up assessment. It could be seen from this information that the analysis of permanent improvement also included patients who did not show permanent improvement, but only a one-off improvement (at the end of the study or without a follow-up assessment). However, the proportion of these patients was not so high as to call into question the interpretability of the analyses on permanent improvement. The company did not provide these data for the outcomes of psychosocial morbidity (PlexiQoL) and health status (EQ-5D VAS). For the outcomes of psychosocial morbidity (PlexiQoL) and health status (EQ-5D VAS), it therefore remained unclear whether a relevant proportion of the events included were merely one-off improvements. The results for the PlexiQoL and the EQ-5D VAS are therefore not presented.

Table 5: Results (morbidity, time to event) – RCT, direct comparison: selumetinib vs. placebo

Study Outcome category Outcome	selumetinib N	selumetinib Median time to event in days [95% CI] Patients with event n (%)	placebo N	placebo Median time to event in days [95% CI] Patients with event n (%)	selumetinib vs. placebo HR [95% CI]; p-value[a]
KOMET					
Morbidity					
Time to permanent improvement					
Chronic pain (NRS[b])	68	NA [252.02; NC][c] 29 (42.7)	74	NA 18 (24.3)	1.98 [1.09; 3.58]; 0.030
Spikes of pain (NRS[b])	71	224.93 [84.92; 280.94][c] 49 (69.0)	74	337.86 [309.85; NC][c] 32 (43.2)	1.97 [1.26; 3.08]; 0.002
Pain interference (PII-pNF[d])	67	NA [169.00; NC] 32 (47.8)	72	NA [341.00; NC] 20 (27.8)	2.02 [1.15; 3.55]; 0.024

a. Cox proportional hazards model with treatment, geographical region and baseline PAINS-pNF score for chronic pain as covariables; p-value from the log-rank test.
b. A decrease by ≥1.5 points from baseline is considered a clinically relevant improvement (scale range: 1 to 10).
c. Institute's calculation (conversion from months to days).
d. A decrease of ≥0.9 points from baseline is considered a clinically relevant improvement (scale range: 0 to 6).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; NRS: numerical rating scale; PAINS-pNF: PAin INtensity Scale for Plexiform Neurofibroma; PII-pNF: Pain Interference Index for Plexiform Neurofibroma; RCT: randomised controlled trial

Appendix B Presentation of the results for the outcomes volume change of the target lesion, as well as chronic pain and spikes of pain, assessed using the PGIS and PGIC

Table 6: Results (morbidity, dichotomous) – RCT, direct comparison: selumetinib vs. placebo

Study Outcome category Outcome	selumetinib N	selumetinib Patients with event n (%)	placebo N	placebo Patients with event n (%)	selumetinib vs. placebo RR [95% CI][a]; p-value[b]
KOMET					
Morbidity					
Improvement at Week 48					
Volume change of the target lesion[c]	51	14 (27.5)	53	2 (3.8)	7.27 [1.74; 30.42]; <0.001
Chronic pain (PGIS[d])	56	20 (51.8)	56	15 (26.8)	1.93 [1.17; 3.19]; 0.007
Spikes of pain (PGIS[d])	56	37 (66.1)	56	24 (42.9)	1.54 [1.08; 2.20]; 0.015
Chronic pain (PGIC 1[e])	57	25 (43.9)	58	12 (20.7)	2.12 [1.18; 3.80]; 0.009
Spikes of pain (PGIC 1[e])	57	23 (40.4)	58	11 (19.0)	2.13 [1.15; 3.95]; 0.015
Chronic pain (PGIC 2[f])	57	35 (61.4)	58	17 (29.3)	2.09 [1.34; 3.28]; <0.001
Spikes of pain (PGIC 2[f])	57	34 (59.7)	58	18 (31.0)	1.92 [1.24; 2.98]; 0.002

a. RR [95% CI] unstratified.
b. Institute's calculation, unconditional exact test (CSZ method according to [5]).
c. A reduction of ≥20% by Week 48 compared with baseline.
d. A decrease of ≥1 point from baseline is considered a clinically relevant improvement (scale range: 0 'no pain' to 4 'severe').
e. Defined as 'very much improved', 'much improved' or 'minimally improved' compared with the last visit is regarded as a clinically relevant improvement (scale range: 1 'very much improved' to 7 'very much worse').
f. A rating of 'very much improved', 'much improved' or 'minimally improved' compared with when starting study medication is regarded as a clinically relevant improvement (scale range: 1 'very much improved' to 7 'very much worse').

CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomised controlled trial; RR: relative risk

Table 7: Results (morbidity, time to event) – RCT, direct comparison: selumetinib vs. placebo

Study Outcome category Outcome	selumetinib N Median time to event in days [95% CI] Patients with event n (%)	placebo N Median time to event in days [95% CI] Patients with event n (%)	selumetinib vs. placebo HR [95% CI]; p-value[a]
KOMET			
Morbidity			
Time to permanent improvement			
Chronic pain (PGIS[b])	67 338.00 [211.00; 344.00] 35 (52.2)	72 NA 24 (33.3)	1.66 [0.98; 2.81]; 0.058
Spikes of pain (PGIS[b])	67 169.00 [111.00; 285.00] 43 (64.2)	72 NA [284.00; NC] 31 (43.1)	1.85 [1.16; 2.95]; 0.007
Chronic pain (PGIC 1[c])	68 340.00 [331.00; NC] 30 (44.1)	74 NA 18 (24.3)	1.91 [1.06; 3.43]; 0.025
Spikes of pain (PGIC 1[c])	68 344.00 [336.00; NC] 28 (41.2)	74 NA 17 (23.0)	1.94 [1.06; 3.55]; 0.028

a. Cox proportional hazards model with treatment, geographical region and baseline PAINS-pNF score for chronic pain as covariables; p-value from the log-rank test.
b. A decrease of ≥1 point from baseline is considered a clinically relevant improvement (scale range: 0 ‘no pain’ to 4 ‘severe’).
c. Defined as ‘very much improved’, ‘much improved’ or ‘minimally improved’ compared with the last visit is regarded as a clinically relevant improvement (scale range: 1 ‘very much improved’ to 7 ‘very much worse’).

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; PAINS-pNF: PAin INtensity Scale for Plexiform Neurofibroma; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; RCT: randomised controlled trial