Selumetinib (plexiform neurofibromas in adults with neurofibromatosis type 1)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Patient and family involvement

No feedback was received within the framework of this dossier assessment.

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Part I: Benefit assessment

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[2] Table numbers start with ‘2’ as numbering follows that of the full dossier assessment.

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSC	best supportive care
CI	confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
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
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NRS	numerical rating scale
PAINS-pNF	PAin INtensity Scale for Plexiform Neurofibroma
PedsQL	Paediatric Quality of Life Inventory
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
PROMIS	Patient-Reported Outcome Measurement Information System
PT	Preferred Term
RCT	randomised controlled trial
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMD	standardized mean difference
SmPC	summary of product characteristics
SOC	System Organ Class
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug selumetinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 17 November 2025.

Research question

The aim of this report is to assess the added benefit of selumetinib in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) for symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of selumetinib

Therapeutic indication	**ACT**[a]
Treatment of symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1	BSC[b]
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 optimized, 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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit.

Study pool and study design

KOMET study

The KOMET study is an ongoing, multicentre, randomized, double-blind phase III pivotal study comparing selumetinib with placebo. The study included adult patients with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas.

A total of 145 patients were enrolled and randomly allocated in a 1:1 ratio to either treatment with selumetinib (N = 71) or placebo (N = 74). Treatment with selumetinib in the intervention

arm was carried out in compliance with the summary of product characteristics (SmPC). In both study arms, any necessary concomitant treatment was permitted.

The KOMET study comprises a randomized, double-blind treatment phase lasting 12 treatment cycles (48 weeks) and an open-label, single-arm phase in which all patients were eligible to receive selumetinib. This phase is still ongoing. The results relevant to this benefit assessment were based on data from the randomized treatment phase.

The primary outcome of the KOMET study is the objective response rate, defined as the proportion of patients with a confirmed complete response of the target lesion or a confirmed partial response, based on independent central review in accordance with the criteria set out by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) working group. Further outcomes in the morbidity and side effects categories were also recorded.

Risk of bias

The risk of bias across outcomes was assessed as low for the KOMET study.

The risk of bias for the results on the outcomes all-cause mortality and discontinuation due to AEs was also rated as low.

For the results on the outcomes morbidity, health status and side effects, with the exception of the outcome discontinuation due to AEs, the risk of bias due to incomplete observations for potentially informative reasons was rated as high.

Results

Mortality

All-cause mortality

No deaths occurred in either of the 2 treatment arms. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Morbidity

Chronic pain (numerical rating scale [NRS])

For the outcome chronic pain a statistically significant difference was found in favour of selumetinib in comparison with placebo. The 95% confidence interval (95% CI) for the standardized mean difference (SMD) was not fully outside the irrelevance range [−0.2; 0.2], however. The effect cannot therefore be inferred to be relevant. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Spikes of pain (NRS)

For the outcome spikes of pain a statistically significant difference was found in favour of selumetinib in comparison with placebo. The 95% CI for the SMD was not fully outside the irrelevance range [−0.2; 0.2], however. The effect cannot therefore be inferred to be relevant. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Pain interference

No suitable data were available for the outcome pain interference. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Psychosocial morbidity (Plexiform Neurofibroma Quality of Life Scale [PlexiQoL])

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

Physical functioning

No suitable data were available for the outcome physical functioning. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Health status (EQ-5D visual analogue scale [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.

Health-related quality of life

Outcomes of the outcome category health-related quality of life were not recorded in the study. There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

Side effects

Serious AEs (SAEs) and discontinuations due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes SAEs or discontinuation due to AEs. There is no hint of greater or lesser harm of selumetinib in comparison with placebo for each of these outcomes; an added benefit is therefore not proven in each case.

Severe AEs

A statistically significant difference to the disadvantage of selumetinib compared with placebo was shown for the outcome severe AEs. There is a hint of greater harm of selumetinib compared with placebo.

Gastrointestinal disorders (SOC, AEs),skin and subcutaneous tissue disorders (SOC, AEs), oedema peripheral (PT, AEs), infections and infestations (SOC, severe AEs), investigations (SOC, severe AEs)

For the outcomes gastrointestinal disorders (System Organ Class [SOC], AEs), skin and subcutaneous tissue disorders (SOC, AEs), oedema peripheral (PT [Preferred Term], AEs), infections and infestations (SOC, severe AEs), and investigations (SOC, severe AEs), there was a statistically significant difference to the disadvantage of selumetinib compared with placebo in each case. There is a hint of greater harm of selumetinib compared with placebo in each case.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug selumetinib versus the ACT was assessed as follows:

Overall, negative effects of selumetinib were found in comparison with the ACT. In the side effects outcome category, there is a hint of greater harm of minor extent for the overall rate of severe AEs. Furthermore, for various specific severe AEs and non-serious/non-severe AEs there is in each case a hint of greater harm of up to major extent.

Given the results for the outcomes of chronic pain and spikes of pain, which showed statistically significant but not relevant advantages for selumetinib, the negative effects relating to side effects were not sufficient for the derivation of a lesser benefit.

In summary, for adult patients with symptomatic, inoperable plexiform neurofibromas in neurofibromatosis type 1, an added benefit of selumetinib versus the ACT BSC is not proven.

Table 3 summarizes the probability and extent of added benefit of selumetinib.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) 'proof', (2) 'indication', (3) 'hint', or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or lesser benefit). For further details see [1,2].

Table 3: 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]	Added benefit not proven

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 optimized, 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 approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of selumetinib in comparison with best supportive care (BSC) as the ACT for symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of selumetinib

Therapeutic indication	**ACT**[a]
Treatment of symptomatic, inoperable plexiform neurofibromas in adult patients with neurofibromatosis type 1	BSC[b]
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 optimized, 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 company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit. This deviated from the company's approach, which specified no minimum duration.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on selumetinib (status: 10 October 2025)
- Bibliographical literature search on selumetinib (last search on 1 September 2025)
- Search of trial registries / trial results databases for studies on selumetinib (last search on 21 August 2025)
- Search on the G-BA website for selumetinib (last search on 21 August 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on selumetinib (last search on 26 November 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: selumetinib vs. BSC

Study	Study category			Available sources		
	Study for the marketing authorization of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
D134BC00001 (KOMET[c])	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The KOMET study was used for the benefit assessment. The study pool was consistent with that selected by the company. The study is described in the following section.

I 3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: selumetinib vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
KOMET	RCT, double-blind, parallel	Adults (≥ 18 years) with neurofibromatosis type 1[b] who have ▪ inoperable[c], symptomatic[d] plexiform neurofibromas ▪ ≥ 1 measurable target lesion[e] ▪ ECOG PS 0 or 1	selumetinib (N = 71) placebo (N = 74)	Screening: ≤ 28 days Treatment: up to 12 cycles of 28 days each (randomized phase)[f, g] Observation: until 30 days after the last dose of the study medication	44 centres in Australia, Brazil, Canada, China, Germany, France, Italy, Japan, Poland, Russia, Spain, United Kingdom and the United States 11/2021–ongoing	Primary: objective response rate Secondary: morbidity, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients with a plexiform neurofibroma and at least one further diagnostic criterion for neurofibromatosis type 1 as per international guidelines [8].
c. Defined as a plexiform neurofibroma that cannot be completely surgically removed without a risk of substantial morbidity (including significant bleeding or damage to nerves and/or surrounding vital structures) as assessed by the investigator.
d. Defined as clinically significant symptoms (e.g. pain, motor dysfunction, disfigurement) caused by the plexiform neurofibroma as judged by the investigator.
e. The target lesion was defined as the clinically most relevant plexiform neurofibroma measurable by volumetric magnetic resonance imaging analysis, as assessed by the investigator.
f. Patients in the comparator arm were able to switch to treatment with selumetinib in the event of disease progression, in accordance with the criteria of the REiNS working group [9].
g. Following the randomized treatment phase, all patients were able to receive selumetinib. This phase is still ongoing.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; N: number of randomized patients; RCT: randomized controlled trial; REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis

Table 7: Characteristics of the interventions – RCT, direct comparison: selumetinib vs. placebo

Study	Intervention	Comparison
KOMET	selumetinib 25 mg/m^2 BSA orally twice daily, as per SmPC [10]	placebo orally twice daily
	Dose modification: ▪ Treatment interruption and dose reduction as per SmPC [10] permitted in the event of unacceptable toxicity[a]	
	Concomitant treatment ▪ Any necessary concomitant treatment is permitted Disallowed ▪ Systemic therapy for plexiform neurofibromas (e.g. chemotherapy, immunotherapy, targeted therapy, biologic therapy, monoclonal antibodies, MEK inhibitors [except selumetinib]) ▪ Radiotherapy for plexiform neurofibromas **Prior treatment** Disallowed ▪ Systemic therapy for plexiform neurofibromas < 4 weeks or 5 half-lives prior to the first dose of study medication (e.g. chemotherapy, immunotherapy, targeted therapy, biologic therapy, monoclonal antibodies, MEK inhibitors) ▪ Any radiotherapy > 6 weeks before the first dose of the study medication	

a. Discontinuation of the study medication following more than 2 dose reductions, the occurrence of a severe AE of CTCAE Grade 4 associated with the study medication, or a dose interruption of ≥ 4 weeks.

AE: adverse event; BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; MEK: mitogen-activated protein kinase; RCT: randomized controlled trial; SmPC: summary of product characteristics

Study design

The KOMET study is an ongoing, multicentre, randomized, double-blind phase III pivotal study comparing selumetinib with placebo. The study had a total randomized treatment phase of 48 weeks (12 cycles of 28 days each).

The study included adult patients with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas. The diagnosis required the presence of a plexiform neurofibroma as well as at least one other diagnostic criterion for neurofibromatosis type 1, in accordance with international recommendations [8]. A plexiform neurofibroma was considered inoperable if it could not be completely surgically removed without a risk of substantial morbidity (including significant bleeding or damage to nerves and/or surrounding vital structures) due to encasement, invasiveness or high vascularity of the plexiform neurofibroma. Patients were considered symptomatic if they presented with clinically significant symptoms caused by the plexiform neurofibroma, as judged by the investigator, such as pain, motor dysfunction or disfigurement. Patients were required to have at least one measurable plexiform neurofibroma, defined as a neurofibroma of at least 3 cm measured in one dimension, which has grown along the length of a nerve and involves multiple fascicles

and branches, and which can be measured using volumetric magnetic resonance imaging (can be seen on at least 3 imaging slices with a reasonably well-defined contour).

Furthermore, patients were required to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, as well as adequate organ and bone marrow function. In addition, stable pain medication for plexiform neurofibromas within the 28 days prior to study enrolment was required. During this 28-day screening period, patients kept an electronic pain diary. According to the inclusion criteria, the chronic pain score had to be documented on at least 4 out of 7 days in at least 2 different weeks.

Patients with a confirmed or suspected malignant glioma or a malignant peripheral nerve sheath tumour were excluded from participation in the study. Patients with low-grade glioma (such as an optic glioma) not requiring systemic therapy or radiation therapy were permitted. Further exclusion criteria included clinically significant cardiovascular disease, ophthalmological conditions such as retinal pigment epithelium detachment, central serous retinopathy or retinal vein occlusion, as well as gastrointestinal disease that would preclude adequate absorption of the study medication.

A total of 145 patients were enrolled and randomly allocated in a 1:1 ratio to either treatment with selumetinib (N = 71) or placebo (N = 74). Randomization was stratified according to the average chronic pain score at the target lesion during the screening period (< 3 vs. ≥ 3, on an 11-point numerical rating scale [NRS] ranging from 0 [no pain] to 10 [maximum pain]) and by geographical region (Europe vs. China vs. Japan vs. the rest of the world [Australia, Brazil, Canada and the United States]).

Treatment with selumetinib in the intervention arm was in compliance with the SmPC [10]. In both study arms, any necessary concomitant treatment was permitted (see the section below on the implementation of ACT).

The KOMET study comprises a randomized, double-blind treatment phase lasting 12 treatment cycles (48 weeks) and an open-label, single-arm phase in which all patients were eligible to receive selumetinib. This phase is still ongoing. During the randomized treatment phase, patients in the comparator arm were able to switch to treatment with selumetinib in the event of disease progression, in accordance with the criteria set out by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) working group [9]. This was the case for 3 patients.

The primary outcome of the KOMET study is the objective response rate by the end of Cycle 16, defined as the proportion of patients with a confirmed complete response of the target lesion or a confirmed partial response, based on independent central review in accordance with the REiNS criteria [9]. The target lesion was defined as the clinically most

relevant plexiform neurofibroma as assessed by the investigator and measurable by volumetric magnetic resonance imaging (MRI) (patients could have more than one clinically relevant plexiform neurofibroma). Further outcomes in the morbidity and side effects categories were also recorded.

Planned data cut-offs within the study

The following data cut-offs were planned for the KOMET study:

- 5 August 2024: prespecified primary analysis planned for the time when all patients had completed the 16th cycle
- 17 March 2025: prespecified primary analysis planned for the time when all patients had completed the 24th cycle

The results relevant to this benefit assessment were based on data from the comparative, randomized 48-week treatment phase of 12 cycles.

Implementation of the ACT

The G-BA designated BSC as the ACT for selumetinib in the treatment of adult patients (> 18 years) with symptomatic, inoperable plexiform neurofibromas. BSC refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.

In accordance with the study protocol, patients were permitted to receive any necessary concomitant treatment. Concomitant medication was to be kept as stable as possible throughout the study, particularly in the case of drugs that might interact with the study medication; however, clinically indicated modifications were permitted at any time and were documented. The available information on prior treatment and concomitant treatment indicated that almost all (100% in the intervention arm versus 93% in the comparator arm) patients in the KOMET study received at least one concomitant treatment. The most common concomitant treatment in both study arms was pain medication (non-opioid analgesics, opioids and gabapentinoids). In addition, glucocorticoids, systemic antihistamines and proton pump inhibitors, amongst others, were used. In addition, a wide range of drugs was used for the treatment of a wide variety of symptoms. Medicines for the treatment of skin symptoms were used notably more frequently in the intervention arm than in the comparator arm (e.g. anti-infectives for acne (42% versus 4%), tetracyclines (41% versus 4%)), although this also included treatment for side effects.

In summary, the concomitant treatments used in KOMET were considered to be a sufficient implementation of the ACT BSC.

Patient characteristics

Table 8 shows the patient characteristics of the included study.

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: selumetinib vs. placebo (multipage table)

Study Characteristic Category	selumetinib N = 71	placebo N = 74
KOMET		
Age [years], mean (SD)	33 (11)	30 (9)
Sex [F/M], %	54/46	43/57
Geographical region, n (%)		
Europe	31 (44)	30 (41)
Rest of the world[a]	22 (31)	23 (31)
China	11 (16)	13 (18)
Japan	7 (10)	8 (11)
Duration of disease [years]		
Time between first diagnosis and first study intervention administration, mean (SD)	23.1 (13.5)	18.6 (12.7)
Time between diagnosis of inoperable plexiform neurofibromas and first study intervention administration, mean (SD)	8.7 (11.4)	8.1 (11.3)
Reasons for the inoperability of plexiform neurofibromas, n (%)		
Close proximity to vital structures	36 (51)	40 (54)
Invasiveness	32 (45)	34 (46)
Encasement of vital structures	19 (27)	25 (34)
High vascularity	19 (27)	25 (34)
Unacceptable risk associated with general anaesthesia	1 (1)	0 (0)
Other	13 (18)	17 (23)
Missing	1 (1)	0 (0)
Volume of the target lesion[b] [mL]		
Median [Q1; Q3]	92.0 [25.0; 355.2]	221.9 [49.7; 529.6]
Mean (SD)	481.0 (1231.0)	539.5 (927.2)
Location of target lesion, n (%)		
Trunk	21 (30)	19 (26)
Trunk/limbs	16 (22)	11 (15)
Limbs	13 (18)	18 (24)
Neck/trunk	8 (11)	11 (15)
Head and neck	7 (10)	5 (7)
Head	5 (7)	7 (10)
Body	1 (1)	2 (3)
Other	0 (0)	1 (1)

Table 8: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: selumetinib vs. placebo (multipage table)

Study **Characteristic** **Category**	**selumetinib** **N = 71**	**placebo** **N = 74**
Symptoms caused by the target lesion, n (%)[c]		
Any symptoms	71 (100)	74 (100)
Pain	62 (87)	61 (82)
Disfigurements caused by plexiform neurofibromas	23 (32)	17 (23)
Impaired movement	19 (27)	19 (26)
Motor weakness	14 (20)	19 (26)
Sensory deficits	8 (11)	13 (18)
Facial motor disorders	7 (10)	3 (4)
Loss of vision	2 (3)	3 (4)
Airway obstruction	2 (3)	3 (4)
Dysphagia	2 (3)	2 (3)
Bowel dysfunction	2 (3)	2 (3)
Hearing loss	2 (3)	0 (0)
Respiratory compromise	1 (1)	1 (1)
Bladder dysfunction	1 (1)	2 (3)
Speech disorders	0 (0)	1 (1)
Other symptoms	12 (17)	19 (26)
Other plexiform neurofibromas, [yes/no], %	25/75	41/59
Treatment discontinuation, n (%)[d,e]	13 (18.3)	9 (12.2)
Study discontinuation, n (%)[f, g]	17 (23.9)	14 (18.9)

a. Includes Australia, Brazil, Canada and United States.
b. The target lesion was defined as the clinically most relevant plexiform neurofibroma measurable by volumetric magnetic resonance imaging analysis, as assessed by the investigator.
c. Patients may have exhibited ≥ 1 symptom.
d. Frequent reasons for treatment discontinuation in the intervention arm vs. comparator arm were (percentages refer to randomized patients): AEs (10% vs. 7%), patient request (6% vs. 5%), lost to follow-up (1% vs. 0%).
e. At the end of the randomized study phase (end of Cycle 12).
f. Frequent reasons for study discontinuation in the intervention arm vs. comparator arm were (percentages refer to randomized patients): AEs (14% vs. 8%), patient request (4% vs. 8%), disease progression (3% vs. 0%).
g. At the time of the planned analysis of the primary outcome at the end of Cycle 16 (5 August 2024).

F: female; M: male; n: number of patients in the category; N: number of randomized (or included) patients; NRS: numerical rating scale; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both study arms of KOMET were largely comparable. The patients were on average 33 and 30 years old, and were predominantly from Europe (44% versus 41%) or from Australia, Brazil, Canada or the United

States (31% versus 31%). The ratio of women to men differed between the treatment arms (proportion of women: 54% versus 43%). In addition, there were slight differences in the time since the initial diagnosis (an average of 23 years versus 19 years). All the patients included in the study had symptomatic, inoperable plexiform neurofibromas. The most common symptom was pain (87% versus 82%), followed by disfigurements caused by plexiform neurofibromas (32% versus 23%) and impaired movement (27% versus 26%). Notable differences were observed in the median volume of the plexiform neurofibromas identified as target lesions by the investigator, with a much smaller median volume in the intervention arm (92 mL versus 222 mL). Furthermore, a further plexiform neurofibroma was more rare in patients in the intervention arm (25% versus 41%).

Treatment was discontinued more frequently in the intervention arm than in the comparator arm (18.3% versus 12.2%). The most common reason for treatment discontinuation was AEs. Study discontinuation was more frequent in the intervention arm than in the comparator arm (23.9% vs. 18.9%). The most common reason was AEs (Table 8).

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: selumetinib vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
KOMET	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was assessed as low for the KOMET study.

Transferability of the study results to the German health care context

In Module 4 B, the company stated that the majority of patients in the KOMET study came from OECD countries (Australia, Canada, France, Germany, Italy, Japan, Poland, Spain, the United Kingdom and the United States). It went on to state that the supportive health care provided in KOMET was entirely comparable to that provided in Germany, and that there was no sign of an effect modification due to the characteristic of geographical region relevant to the conclusion. Overall, from the company's perspective, there was nothing to limit the transferability of the results of KOMET to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - Chronic pain recorded using an NRS
  - Spikes of pain recorded using an NRS
  - Pain interference
  - Psychosocial morbidity recorded using the Plexiform Neurofibroma Quality of Life Scale (PlexiQoL)
  - Physical functioning
  - Health status recorded using the visual analogue scale (VAS) of the EQ-5D
- Health-related quality of life
- Side effects
  - Serious adverse events (SAEs)
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Gastrointestinal disorders (System Organ Class [SOC] gastrointestinal disorders, AEs)
  - Skin and subcutaneous tissue disorders (SOC skin and subcutaneous tissue disorders, AEs)
  - Other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 B).

Table 10 shows for which outcomes data were available in the included study.

Table 10: Matrix of outcomes – RCT, direct comparison: selumetinib vs. placebo

Study	Outcomes													
	All-cause mortality[a]	Chronic pain (NRS)	Spikes of pain (NRS)	Pain interference	Psychosocial morbidity (PlexiQoL)	Physical functioning	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AEs)	Skin and subcutaneous tissue disorders (SOC, AEs)	Other specific AEs[c]
KOMET	Yes	Yes	Yes	No[e]	Yes	No[e]	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Severe AEs are operationalized as CTCAE ≥ 3.
c. The following events are considered (coded according to MedDRA): oedema peripheral (PT, AEs), infections and infestations (SOC, severe AEs), and investigations (SOC, severe AEs).
e. No suitable data available; see the following text sections for reasons.
f. Outcomes in this category were not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; NRS: numerical rating scale; PlexiQoL: Plexiform Neurofibroma Quality of Life Scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Outcome: volume change of the target lesion

In the given therapeutic indication, plexiform neurofibromas cause symptoms for patients. Due to its mechanism of action, selumetinib is a disease-modifying treatment. A reduction in tumour size may potentially lead to an alleviation of symptoms.

In its dossier, the company presented various analyses of volume change of the target lesion (absolute/percentage volume change of the target lesion compared with baseline; the best percentage volume change of the target lesion achieved; and patients with a volume reduction of the target lesion of ≥ 20% compared with baseline). These analyses were not used for the benefit assessment. This is explained below.

To record the outcome volume change in KOMET, a volumetric MRI analysis was carried out by the investigator on the plexiform neurofibroma selected as the target lesion. The assessment was carried out in accordance with the criteria set out by the REiNS working group. These recommend a 20% reduction or increase in volume as a response criterion for assessing treatment response and disease progression, as this is regarded as a suitable threshold value for the reproducible detection of small changes in volume [9].

When assessing the results for the volume change outcome, a number of uncertainties must be taken into account. As described by the REiNS group, volumetric MRI analysis is generally suitable for determining changes in the volume of plexiform neurofibromas. However, plexiform neurofibromas are often very complex and diffuse morphologies which can sometimes be difficult to distinguish from the surrounding tissue on an MRI, and which may exhibit naturally occurring fluctuations in volume due to external factors [9]. Consequently, there are uncertainties as to the extent to which accurate and reproducible volumetric measurements can be reliably carried out for all selected target lesions, so as to be able to represent even small changes in volume in the low percentage range. Furthermore, in addition to the lesions analysed, patients may have other clinically relevant plexiform neurofibromas that are not included in the analyses presented.

Notwithstanding the uncertainties described, in the given operationalization the volume change outcome was not considered patient-relevant. This is described below.

Patient relevance of the volume change outcome

Depending on their size and location, plexiform neurofibromas can cause a wide variety of symptoms. Common symptoms, some of which can be serious, may include, for example, pain, motor impairments and functional impairments affecting various internal organs. Lesions in visible areas can also cause notable disfigurement. This can have a relevant impact on patients' quality of life, for example in the form of psychological distress and limitations in their daily lives.

Overall, it is therefore understandable that a reduction in the volume of plexiform neurofibromas can lead to a tangible improvement in symptoms and health-related quality of life.

However, the extent to which the tumour must be reduced in order to bring about such a tangible improvement varies from patient to patient and depends, in particular, on the size and location of the plexiform neurofibromas. It is therefore not possible, on the basis of a percentage change alone, to draw a conclusion about the effects of the reduction in volume on symptoms and health-related quality of life in individual patients. Only in the event of complete regression of the plexiform neurofibroma could one be certain that there would be a patient-relevant improvement in the associated symptoms.

The company dossier presented, amongst other things, results relating to outcome operationalizations using a response threshold of 20% in accordance with the REiNS criteria. This criterion was selected solely for the sake of the reproducibility of the measurement results [9]. The patient relevance of volume change was not taken into account in this context. Rather, the REiNS group points out that no correlation has been shown between a response seen on imaging and clinical improvement, and therefore recommends that further outcomes,

such as patient-reported outcomes (PROs), be recorded when conducting clinical studies (see below).

For the benefit assessment, therefore, data showing what an observed reduction in volume actually means for patients would be crucial. The volume change outcome for the target lesion alone was not used for the benefit assessment.

Objective response rate outcome

The primary outcome – the objective response rate – in the KOMET study was operationalized as a composite outcome comprising the proportion of patients with a confirmed complete response or a confirmed partial response (tumour volume decrease ≥ 20% of the target lesion [plexiform neurofibroma] compared with baseline).

As described above, in the event of complete regression of the plexiform neurofibroma it is certain that there is a patient-relevant improvement in the associated symptoms. However, the data in Module 4 B show that no patient achieved a complete response. The patient relevance of a partial response (i.e. a reduction in tumour volume of ≥ 20%, as shown by imaging techniques alone) cannot be assessed without further information. The outcome objective response rate was therefore not used for the benefit assessment.

Pain analyses presented by the company

Chronic pain and spikes of pain

Pain is an important symptom of plexiform neurofibromas, which often persists despite the use of painkillers [11]. Both chronic pain and sudden, episodic pain flare-ups (‘spikes of pain’) can be a burden for patients and restrict their daily lives [12]. The outcomes chronic pain and spikes of pain are therefore assessed as patient-relevant in this indication.

The company provided analyses of the PAin INtensity Scale for Plexiform Neurofibroma (PAINS-pNF) for both chronic pain and spikes of pain; this scale was specifically developed by the National Cancer Institute (NCI), in collaboration with patients with neurofibromatosis type 1, to assess the pain symptoms caused by plexiform neurofibromas [12]. For this, data is recorded daily using an electronic diary. Pain is assessed in relation to a target lesion identified by a doctor. Chronic pain and pain peaks are each assessed using an 11-point NRS (0 [no tumour pain] to 10 [maximum possible tumour pain]). These were assessed as suitable for the given therapeutic indication for recording spikes of pain and chronic pain caused by plexiform neurofibromas.

In KOMET, the maximum value recorded in the electronic diary entries for a single cycle (28 days) was used for pain peaks. For chronic pain, an average was calculated over 28 days. Differing minimum requirements were used: For the screening phase, the average was based on diary entries for at least 4 out of 7 days in at least 2 different weeks; during the study, it

was based on entries for at least 4 out of 7 days in at least 3 different weeks. The operationalizations of chronic pain and pain peaks recorded using the NRS thus each capture patient-reported pain scores over an entire 28-day cycle.

In addition, the company provided further analyses for the outcomes spikes of pain and chronic pain, based on the Patient Global Impression of Severity (PGIS) and the Patient Global Impression of Change (PGIC). Unlike the NRS scales described above, the PGIS and PGIC were used to record changes in chronic pain and spike pain only at individual visits within a cycle. The PGIS and PGIC were therefore not taken into account in this benefit assessment.

Pain relief for chronic pain

The company also presented analyses for the outcome pain relief, defined as chronic pain recorded on the basis of the NRS for chronic pain (see above) and the additional condition that there was no increase in pain medication. This outcome was not used for the benefit assessment, as chronic pain was already adequately represented by the NRS.

Pain interference

The outcome 'pain interference' is relevant in this therapeutic indication. The company presented operationalizations recorded using the Pain Interference Index for Plexiform Neurofibroma (PII-pNF) [12]. At baseline, over 30% (34% versus 32%) of patients in both treatment arms did not have fully completed questionnaires, meaning that the validity of the data presented was unclear. The analyses submitted by the company on the outcome of pain interference were therefore not taken into account in the benefit assessment.

Psychosocial morbidity recorded using the PlexiQoL

Some patients with plexiform neurofibromas report major disease-related impairments to their physical appearance, their social relationships and their independence in everyday life [13]. Accordingly, the outcome psychosocial morbidity is generally assessed as relevant in this therapeutic indication.

In its dossier, the company presented analyses from the PlexiQoL and classified them under the heading of health-related quality of life. Scales used to record health-related quality of life should take into account the impact of the condition on psychological, physical and social functioning / well-being, and should represent at least these 3 dimensions. However, the PlexiQoL only measures social and psychological aspects in patients with plexiform neurofibromas in neurofibromatosis type 1 and is therefore classified within morbidity. The PlexiQol consists of 18 items, each of which is answered with 'true' (1 point) or 'not true' (0 points). A total score is calculated. A higher score means a higher level of psychosocial stress [14]. Recording was performed electronically at the time of screening, at baseline and, during

the randomized phase, on Day 28 of Cycles 2, 4, 8 and 12, or in the event of premature discontinuation of treatment. PlexiQol was used for the benefit assessment.

Physical functioning

Physical functioning was assessed as a relevant outcome in this therapeutic indication [15]. In KOMET, physical functioning was recorded using 3 items from the Physical Function Short Form 8c (PF8c; v2.0) [16] of the Patient-Reported Outcome Measurement Information System (PROMIS). The full PROMIS-PF8c comprises 8 items designed for the recording of physical functioning. In the given therapeutic indication, this generic instrument is suitable for recording patients' perceived physical function. The company did not justify the selection of the 3 items. It is not appropriate to select individual items from a validated instrument. The analyses presented by the company were therefore disregarded for the benefit assessment.

Skin sensations recorded using the Paediatric Quality of Life Inventory (PedsQL)

In its dossier, the company presented analyses of 3 items on skin sensations, taken from the PedsQL Neurofibromatosis Module, version 3.0 (version for young adults) [17].

The company did not explain why it recorded data on only 3 items and not the entire questionnaire. The PedsQL Neurofibromatosis Module was developed in collaboration with patients and is fully validated for the therapeutic indication of neurofibromatosis type 1. The instrument includes items relating to various symptom clusters associated with neurofibromatosis type 1, including pain, skin itch bother, skin sensations, cognitive functioning, speech, fine motor, balance and vision. It is not appropriate to select individual items from a validated instrument. The analyses presented by the company were disregarded for the benefit assessment.

Analysis of the PROs relating to morbidity

For patients with symptomatic, inoperable plexiform neurofibromas in neurofibromatosis type 1, a sustained improvement in symptoms is a relevant treatment goal. Plexiform neurofibromas usually show slow, progressive tumour growth in adulthood [18]. The mean time since diagnosis of inoperable, symptomatic plexiform neurofibroma was approximately 9 versus 8 years among the patients in the KOMET study. Consequently, the chronic, progressive symptoms caused by the tumour's growth had already been present for some time. Given the long-term course of disease, a sustained improvement in symptoms is regarded as a relevant treatment goal versus merely a short-term improvement (for example, lasting just a few weeks)[12]. Accordingly, when assessing the content of the PRO analyses submitted by the company, consideration was given to the extent to which the reduction in the burden of symptoms was represented over a sufficiently long period.

In Module 4 B, the company presented time-to-event analyses for the included PROs relating to morbidity, in each case for the time to first improvement and for the time to first deterioration of ≥ 15% of the scale range. In addition, the company provided supplementary analyses of continuous data using a mixed-effects model with repeated measures (MMRM) in Module 4, Appendix 4 G. The analysis of patient-reported outcomes using MMRM analyses was specified in the study protocol.

The time-to-event analyses provided were not taken into account in the benefit assessment. In the operationalizations of the time to the first improvement presented by the company, it remained unclear whether an improvement is long-term and can therefore be assessed as relevant. In this therapeutic indication, it would be useful to present responder analyses (of improvement) for the PROs for the end of the randomized study phase (Week 48). As explained in the IQWiG *General Methods* [19], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified and exactly 15% of the scale range in post-hoc analyses.

As no responder analyses were available in the company dossier for the end of the randomized study phase, the MMRM analyses of the PROs were used for the benefit assessment.

I 4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: selumetinib vs. placebo

Study		Outcomes													
	Study level	All-cause mortality[a]	Chronic pain (NRS)	Spikes of pain (NRS)	Pain interference	Psychosocial morbidity (PlexiQoL)	Physical functioning	Health status (EQ-5D VAS)	Health-related quality of life	SAEs	Severe AEs[b]	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AEs)	Skin and subcutaneous tissue disorders (SOC, AEs)	Other specific AEs[c]
KOMET	L	L	H[d]	H[d]	–[e]	H[d]	–[e]	H[d]	–[f]	H[d]	H[d]	L	H[d]	H[d]	H[d]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. The following events are considered (coded according to MedDRA): oedema peripheral (PT, AEs), infections and infestations (SOC, severe AEs), and investigations (SOC, severe AEs).
d. Incomplete observation period for potentially informative reasons.
e. No suitable data available; see Section I 4.1 for the reasoning.
f. Outcomes in this category were not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NRS: numerical rating scale; PlexiQoL: Plexiform Neurofibroma Quality of Life Scale; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Risk of bias for the results of the relevant outcomes

The risk of bias for the results on the outcomes all-cause mortality and discontinuation due to AEs was rated as low.

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 randomized 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 the outcomes relating to morbidity, health status and side effects – with the exception of the outcome discontinuation due to AEs – owing to the incomplete observation period due to potentially informative reasons.

I 4.3 Results

Table 12 and Table 13 summarize the results of the comparison of selumetinib and placebo in adult patients with symptomatic, inoperable plexiform neurofibromas in neurofibromatosis

type 1. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results on common AEs, SAEs and discontinuation due to AEs are presented in I Appendix B of the full dossier assessment.

Table 12: Results (mortality, health-related quality of life, side effects) – RCT, direct comparison: selumetinib vs. placebo

Study Outcome category Outcome	selumetinib		placebo		selumetinib vs. placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][a] p-value[b]
KOMET					
Mortality					
All-cause mortality[c]	71	0 (0)	74	0 (0)	–
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	71	71 (100)	74	68 (91.9)	–
SAEs	71	10 (14.1)	74	9 (12.2)	1.16 [0.50; 2.68]; 0.775
Severe AEs[d]	71	23 (32.4)	74	13 (17.6)	1.84 [1.01; 3.35]; 0.043
Discontinuation due to AEs	71	9 (12.7)	74	5 (6.8)	1.88 [0.66; 5.33]; 0.254
Gastrointestinal disorders (SOC, AEs)	71	53 (74.7)	74	32 (43.2)	1.73 [1.29; 2.32]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	71	64 (90.1)	74	26 (35.1)	2.57 [1.86; 3.53]; < 0.001
Oedema peripheral (PT, AEs)	71	11 (15.5)	74	1 (1.4)	11.46 [1.52; 86.52]; 0.002
Infections and infestations (SOC, severe AEs[d])	71	6 (8.5)	74	1 (1.4)	6.25 [0.77; 50.65]; 0.048
Investigations (SOC, severe AEs[d])	71	10 (14.1)	74	1 (1.4)	10.42 [1.37; 79.33]; 0.005

a. RR [95% CI] unstratified
b. Institute's calculation, unconditional exact test (CSZ method according to [20]).
c. The results on all-cause mortality are based on the data on fatal AEs.
d. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Table 13: Results (morbidity) – RCT, direct comparison: selumetinib vs. placebo

Study Outcome category Outcome	selumetinib			placebo			selumetinib vs. placebo
	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SE)	MD [95% CI]; p-value
KOMET							
Morbidity							
Chronic pain (NRS)[c]	68	4.2 (2.5)	−1.29 (0.2)	74	4.3 (2.7)	−0.8 (0.2)	−0.48 [−0.95; −0.01]; 0.048 SMD: −0.33 [−0.66; −0.01][d]
Spikes of pain (NRS)[c]	71	6.6 (2.6)	−1.9 (0.2)	74	6.3 (3.0)	−1.3 (0.2)	−0.62 [−1.20; −0.05]; 0.033 SMD: −0.34 [−0.67; −0.01]
Pain interference	No suitable data[e]						
Psychosocial morbidity (PlexiQoL)[f,g]	64	9.3 (4.7)	−0.7 (0.4)	71	8.1 (4.1)	−0.6 (0.4)	-0.03 [-0.96; 0.90]; 0.949
Physical functioning	No suitable data[e]						
Health status (EQ-5D VAS)[g, h]	64	63.5 (19.1)	6.4 (1.7)	71	62.1 (21.2)	5.6 (1.6)	0.74 [−3.30; 4.79]; 0.716

a. Number of patients taken into account in the effect estimation; values at baseline (and at the end of the randomized treatment phase) may be based on different patient numbers.
b. MMRM with treatment, cycle and region as fixed effects, baseline value as a continuous covariate, and the interaction terms between treatment and cycle, and between baseline value and cycle.
c. Lower (decreasing) values indicate less pain; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 1 to 10).
d. Institute's calculation, differs from data from the company in Module 4 B.
e. See Section I 4.1 for reasons.
f. Lower (decreasing) values indicate lower psychosocial morbidity; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 1 to 18).
g. MMRM with treatment, baseline value, cycle, baseline value for chronic pain in the target lesion and region as covariates, and the interaction terms between treatment and cycle, and between baseline value and cycle.
h. Higher (increasing) values indicate better health status; positive effects (intervention minus comparison) indicate an advantage for the intervention (scale range: 0 to 100).

CI: confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; NRS: numerical rating scale; PlexiQoL: Plexiform Neurofibroma Quality of Life Scale; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

No deaths occurred in either of the 2 treatment arms. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Morbidity

Chronic pain (NRS)

For the outcome chronic pain a statistically significant difference was found in favour of selumetinib in comparison with placebo. The 95% confidence interval (95% CI) for the standardized mean difference (SMD) was not fully outside the irrelevance range [−0.2; 0.2], however. The effect cannot therefore be inferred to be relevant. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Spikes of pain (NRS)

For the outcome spikes of pain a statistically significant difference was found in favour of selumetinib in comparison with placebo. The 95% CI for the SMD was not fully outside the irrelevance range [−0.2; 0.2], however. The effect cannot therefore be inferred to be relevant. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; an added benefit is therefore not proven.

Pain interference

No suitable data were available for the outcome pain interference. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; 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. There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

Physical functioning

No suitable data were available for the outcome physical functioning. There is no hint of an added benefit of selumetinib compared with placebo for this outcome; 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.

Health-related quality of life

Outcomes of the outcome category health-related quality of life were not recorded in the study. There is no hint of an added benefit of selumetinib compared with placebo; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

No statistically significant difference between treatment groups was found for either of the outcomes SAEs or discontinuation due to AEs. There is no hint of greater or lesser harm of selumetinib in comparison with placebo for each of these outcomes; an added benefit is therefore not proven in each case.

Severe AEs

A statistically significant difference to the disadvantage of selumetinib compared with placebo was shown for the outcome severe AEs. There is a hint of greater harm of selumetinib compared with placebo.

Gastrointestinal disorders (SOC, AEs),skin and subcutaneous tissue disorders (SOC, AEs), oedema peripheral (PT, AEs), infections and infestations (SOC, severe AEs), investigations (SOC, severe AEs)

For the outcomes gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), oedema peripheral (PT [Preferred Term], AEs), infections and infestations (SOC, severe AEs), and investigations (SOC, severe AEs), there was a statistically significant difference to the disadvantage of selumetinib compared with placebo in each case. There is a hint of greater harm of selumetinib compared with placebo in each case.

I 4.4 Subgroups and other effect modifiers

The following subgroup characteristics were taken into account in this benefit assessment:

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

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results did not show any relevant effect modifications.

I 5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [19].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 5.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Chapter I 4 (see Table 14).

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.

Morbidity

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

For the outcomes chronic pain and spikes of pain, 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 14: Extent of added benefit at outcome level: selumetinib vs. BSC (multipage table)

Outcome category **Outcome**	**selumetinib vs. placebo** **Proportion of events (%) or mean change in the course of the study** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0% RR: –	Lesser benefit not proven / added benefit not proven
Morbidity		
Chronic pain (NRS)	−1.29 vs. −0.8 MD: −0.48 [−0.95; −0.01]; p = 0.048 SMD: −0.33 [−0.66; −0.01][c]	Lesser benefit not proven / added benefit not proven
Spikes of pain (NRS)	−1.9 vs. −1.3 MD: −0.62 [−1.20; −0.05]; p = 0.033 SMD: −0.34 [−0.67; −0.01][c]	Lesser benefit not proven / added benefit not proven
Pain interference	No suitable data	Lesser benefit not proven / added benefit not proven
Psychosocial morbidity (PlexiQoL)	−0.7 vs. −0.6 MD: −0.03 [−0.96; 0.90]; p = 0.949	Lesser benefit not proven / added benefit not proven
Physical functioning	No suitable data	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS)	6.4 vs. 5.6 MD: 0.74 [−3.30; 4.79]; p = 0.716	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
Outcomes from this category were not recorded		
Side effects		
SAEs	14.1% vs. 12.2% RR: 1.16 [0.50; 2.68]; p = 0.775	Greater/lesser harm not proven
Severe AEs	32.4% vs. 17.6% RR: 1.84 [1.01; 3.35] RR: 0.54 [0.30; 0.99][d]; p = 0.043 Probability: hint	Outcome category: Serious/severe side effects $CI_u < 1.00$ Greater harm, extent: minor
Discontinuation due to AEs	12.7% vs. 6.8% RR: 1.88 [0.66; 5.33]; p = 0.254	Greater/lesser harm not proven

Table 14: Extent of added benefit at outcome level: selumetinib vs. BSC (multipage table)

Outcome category **Outcome**	**selumetinib vs. placebo** **Proportion of events (%) or mean change in the course of the study** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Gastrointestinal disorders (SOC, AEs)	74.7% vs. 43.2% RR: 1.73 [1.29; 2.32] RR: 0.58 [0.43; 0.78][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Skin and subcutaneous tissue disorders (SOC, AEs)	90.1% vs. 35.1% RR: 2.57 [1.86; 3.53] RR: 0.39 [0.28; 0.54][d]; p < 0.001 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Oedema peripheral (PT, AEs)	15.5% vs. 1.4% RR: 11.46 [1.52; 86.52] RR: 0.09 [0.01; 0.66][d]; p = 0.002 Probability: hint	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Infections and infestations (SOC, severe AEs)	8.5% vs. 1.4% RR: 6.25 [0.77; 50.65] RR: 0.16 [0.02; 1.30][d]; p = 0.048	Outcome category: serious/severe side effects Greater harm[e], extent: minor[f]
Investigations (SOC, severe AEs)	14.1% vs. 1.4% RR: 10.42 [1.37; 79.33] RR: 0.10 [0.01; 0.73][d]; p = 0.005 Probability: hint	Outcome category: Serious/severe side effects CI_u < 0.75 and risk ≥ 5% Greater harm, extent: major

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).
c. If the CI for the SMD is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The result of the statistical test is decisive for the derivation of the added benefit.
f. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_L: lower limit of the confidence interval; CI_u: upper limit of the confidence interval; MD: mean difference; MMRM: mixed-effects model with repeated measures; NRS: numerical rating scale; PlexiQoL: Plexiform Neurofibroma Quality of Life Scale; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 15 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 15: Positive and negative effects from the assessment of selumetinib in comparison with BSC

Positive effects	**Negative effects**
–	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 outcomes pain interference and physical functioning. Outcomes on health-related quality of life were not recorded.	
AE: adverse event	

Overall, negative effects of selumetinib were found in comparison with the ACT. In the side effects outcome category, there is a hint of greater harm of minor extent for the overall rate of severe AEs. Furthermore, for various specific severe AEs and non-serious/non-severe AEs there is in each case a hint of greater harm of up to major extent.

Given the results for the outcomes of chronic pain and spikes of pain, which showed statistically significant but not relevant advantages for selumetinib, the negative effects relating to side effects were not sufficient for the derivation of a lesser benefit.

In summary, for adult patients with symptomatic, inoperable plexiform neurofibromas in neurofibromatosis type 1, an added benefit of selumetinib versus the ACT BSC is not proven.

The result of the assessment of the added benefit of selumetinib in comparison with the ACT is summarized in Table 16.

Table 16: 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]	Added benefit not proven

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 optimized, 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 assessment described above deviates from that of the company, which derived an indication of a considerable added benefit based on the KOMET study.

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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