

Selumetinib (plexiform neurofibromas in neurofibromatosis type 1, ≥ 3 to < 18 years)

Benefit assessment according to §35a SGB V¹

A horizontal bar composed of 18 squares of varying shades of blue and grey. The word 'EXTRACT' is centered in white text on a dark blue segment of the bar.

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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
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MRI	magnetic resonance imaging
RCT	randomized controlled trial
REINS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics

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 as the appropriate comparator therapy (ACT) for symptomatic, inoperable plexiform neurofibromas in paediatric patients with neurofibromatosis type 1 aged 3 years and older.

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 paediatric patients with neurofibromatosis type 1 aged 3 years and older	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. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

Consistent with the findings of the company, a review of the completeness of the study pool did not identify any randomized controlled trials (RCTs) for the comparison of selumetinib with the ACT.

As the company did not identify any studies for a direct comparison, it conducted information retrievals for further studies on selumetinib and the ACT. For selumetinib, it identified the single-arm pivotal study SPRINT, as well as the single-arm studies D1346C00013,

D1346C00011, D1346C00015, SPRINKLE and ESR-17-12847. Furthermore, on the comparator side, it identified 5 studies on the natural course of the disease by Fisher 2008, Kotch 2023, Nguyen et al. 2012, Nguyen 2013 and Well 2021, for which it presented the relevant publications. The company drew on these studies as what it considered to be the best available evidence for the assessment of the added benefit.

No review of the completeness of the study pool for further investigations was conducted, as the data provided by the company were not suitable for the benefit assessment. This is explained below.

Evidence provided by the company

In its dossier, the company presented the results of the respective single-arm studies on selumetinib. For the ACT best supportive care it presented only data on the annual growth rate of plexiform neurofibromas from the publications it identified on the natural course of the disease. The results section of the dossier did not contain any comparative analyses between selumetinib and the ACT. The following section describes the limitations of the studies presented on selumetinib and on the ACT, and explains why comparability was limited.

Studies on selumetinib

The pivotal study SPRINT is a single-arm study sponsored by the National Cancer Institute Cancer Therapy Evaluation Program, evaluating selumetinib in children and adolescents aged 2 to 18 years with neurofibromatosis type 1 and inoperable plexiform neurofibromas.

The 5 further studies on selumetinib cited by the company were all single-arm studies, which predominantly enrolled children and adolescents aged between 3 and 18 years with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas.

The patient populations of the pivotal study SPRINT considered by the company and the studies D1346C00013 and D1346C00011 largely corresponded to the therapeutic indication under assessment; however, as the studies were conducted exclusively in the United States and Asia, there were uncertainties regarding the transferability of the study results to the German health care context.

For the studies D1346C00015, ESR-17-12847 and SPRINKLE, however, it was unclear whether, and if so to what extent, patients outside the therapeutic indication were included in the respective population presented by the company (D1346C00015, ESR-17-12847: inclusion of patients whose plexiform neurofibromas do not cause any symptoms also possible; SPRINKLE: children < 3 years of age). Furthermore, D1346C00015 had a very short observation period, falling short of the minimum study duration of 24 weeks. Due to the age restrictions, D1346C00015 and SPRINKLE also represented only a subpopulation of the therapeutic

indication. Overall, D1346C00015, SPRINKLE and ESR-17-12847 were therefore not suitable for the benefit assessment.

Studies on the ACT

On the comparator side, the company presented data from 5 studies on the natural course of the disease to characterize the annual growth rate of plexiform neurofibromas. Given that the ACT determined by the G-BA – best supportive care – is used as a supportive treatment to alleviate symptoms or improve quality of life, and does not result in a reduction in the volume of plexiform neurofibromas, it is reasonable to present data on the natural course of the disease in terms of growth rates of plexiform neurofibromas on the comparator side. No data were presented on the comparator side for any other outcomes.

The company explained that, in the studies on the comparator side, positive growth rates of plexiform neurofibromas were observed in a large proportion of patients over the course of the disease, and a reduction in volume occurred only very rarely. This is consistent with other publications which indicate that, whilst a spontaneous reduction in the volume of plexiform neurofibromas is in principle possible, it occurs only rarely, particularly in children. It was also discussed during the oral hearings on the orphan drug procedure for selumetinib that spontaneous remission does not usually occur in the natural course of the disease. However, the results presented by the company were subject to uncertainties, which are explained below.

The company merely submitted the relevant publications relating to the studies, but not the study protocols or clinical study reports. The dossier therefore lacked important information on how the studies were conducted and, in particular, on the baseline characteristics of the study populations – such as characteristics of the plexiform neurofibromas – which would be necessary to assess the relevance of the studies. Overall, the comparability with the studies on selumetinib was insufficient / due to a lack of information, the comparability could not be adequately assessed. Based on the information provided it was not possible to determine what proportion of the respective populations had symptomatic and unresectable plexiform neurofibromas at baseline, in line with the therapeutic indication. Nor do the publications provided contain sufficient information regarding the use of best supportive care. Further limitations arose from the fact that in some studies only a subpopulation of the therapeutic indication to be assessed was analysed, for which it remains unclear whether the results can be transferred to the entire therapeutic indication, and it is also questionable whether these patients are sufficiently similar versus the populations in the studies involving selumetinib.

Irrespective of the aspects mentioned regarding the study populations and the associated questions in terms of similarity and transferability, the company only reported results relating to the annual growth rates of plexiform neurofibromas from the studies on the ACT. As

described in the following sections, outcomes that only consider a volume change to plexiform neurofibromas are not regarded as patient-relevant. Overall, it was therefore not possible to carry out the comprehensive assessment required as part of the benefit assessment, taking into account data on outcomes relating to the morbidity, health-related quality of life and side effects categories. Consequently, the studies / subpopulations within these studies assessed by the company were not suitable for the benefit assessment.

Summary

As described, the company merely provided descriptive presentations of the results from the single-arm studies on selumetinib in the dossier; the results section of the dossier did not contain any effect estimates for comparison with the ACT. On the comparator side, the company only presented annual growth rates of plexiform neurofibromas which it had extracted, which enable the classification of the effects of selumetinib.

Overall, therefore, no comparative evidence suitable for the benefit assessment of selumetinib versus the ACT was available. Furthermore, there were uncertainties in the publications submitted by the company regarding the characterization of the natural course of the disease. This related in particular to the questionable similarity between the studies on the selumetinib side and those on the comparator side, the inclusion of patients outside the relevant therapeutic indication, the lack of information on the implementation of best supportive care in the studies on the comparator side, as well as the issues of transferability mentioned and the lack of results on patient-relevant outcomes.

Notes on the volume change outcome

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. As previously described, spontaneous volume reduction is rare in children during the natural course of the disease, and no disease-modifying drug has been available to date.

However, the volume change outcome is not suitable for benefit assessment in the operationalization presented. This is explained below.

To record the outcome volume change in the selumetinib studies, a volumetric magnetic resonance imaging (MRI) analysis was carried out by the investigator on the plexiform neurofibroma selected as the target lesion. The target lesion was defined as the most clinically relevant plexiform neurofibroma suitable for volumetric MRI analysis. The assessment was carried out in accordance with the criteria of the Response Evaluation in Neurofibromatosis and Schwannomatosis (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. Accordingly, the studies on selumetinib recorded, amongst other things, the proportion of patients who experienced a $\geq 20\%$ reduction in the volume of the target lesion.

When assessing the results for the volume change outcome, a number of uncertainties must be taken into account. Whilst volumetric MRI analysis is, in principle, suitable for determining volume changes in plexiform neurofibromas, there are uncertainties as to the extent to which accurate and reproducible volumetric measurements can be reliably carried out on all selected target lesions, so as to be able to represent even small percentage changes in volume. 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, some of which may be serious, such as pain, motor impairments, functional impairment of various internal organs and disfigurement. 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.

For the benefit assessment, therefore, data showing what an observed reduction in volume actually means for patients would be crucial. In the given context, in which spontaneous volume reduction occurs only very rarely in the natural course of the disease, data on the volume change outcome from single-arm studies can therefore only be taken into account if a reduction in volume is accompanied by a relevant improvement in symptoms and/or quality of life, as measured using a validated instrument. This could be achieved if, in the analysis, reductions in volume were linked to a recording of symptoms and/or health-related quality of life. The company dossier contained results for numerous patient-reported outcomes in these categories. One possible approach, for example, would be to use an analysis as an outcome that, in addition to a reduction in the volume of the target lesion, also incorporates appropriate patient-reported outcomes, thereby allowing conclusions to be reached about possible improvements in symptoms and/or the patients' quality of life associated with the reduction in volume. Consideration would also need to be given to selecting a suitable timepoint at which both recordings of changes in volume and recordings of symptoms or

health-related quality of life are available, whilst ensuring that the minimum study duration of 24 weeks is observed. However, such an operationalization was not planned in the studies presented.

Furthermore, an overall assessment would also require suitable data on outcomes relating to side effects.

Results on added benefit

No suitable data were available to assess the added benefit of selumetinib compared with the ACT, best supportive care, for the treatment of symptomatic, inoperable plexiform neurofibromas in paediatric patients with neurofibromatosis type 1 aged 3 years and older. There is thus no hint of an added benefit of selumetinib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

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

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 paediatric patients with neurofibromatosis type 1 aged 3 years and older	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 G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the result of the G-BA's assessment conducted in the context of the market launch in 2021 and the reassessment following the expiry of the

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].

decision in 2023. In those assessments, the G-BA had determined a non-quantifiable added benefit of selumetinib. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of selumetinib in comparison with best supportive care as the ACT for symptomatic, inoperable plexiform neurofibromas in paediatric patients with neurofibromatosis type 1 aged 3 years and older.

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 paediatric patients with neurofibromatosis type 1 aged 3 years and older	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. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit.

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: 22 September 2025)
- Bibliographical literature search on selumetinib (last search on 22 September 2025)
- Search of trial registries / trial results databases for studies on selumetinib (last search on 22 September 2025)
- Search on the G-BA website for selumetinib (last search on 22 September 2025)
- Bibliographical literature search on the ACT (last search on 22 September 2025)
- Search of trial registries / trial results databases for studies on the ACT (last search on 22 September 2025)
- Search on the G-BA website for the ACT (last search on 22 September 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

Consistent with the findings of the company, a review of the completeness of the study pool did not identify any randomized controlled trials (RCTs) for the comparison of selumetinib with the ACT.

As the company did not identify any studies for a direct comparison, it conducted information retrievals for further studies on selumetinib and the ACT. For selumetinib, it identified the single-arm pivotal study SPRINT [3], and the single-arm studies D1346C00013 [4], D1346C00011 [5], D1346C00015 [6], SPRINKLE [7] and ESR-17-12847 [8]. Furthermore, on the comparator side, it identified 5 studies on the natural course of the disease: Fisher 2008 [9], Kotch 2023 [10], Nguyen 2012 [11], Nguyen 2013 [12] and Well 2021 [13], for which it provided the relevant publications. The company drew on these studies as what it considered to be the best available evidence for the assessment of the added benefit.

No review of the completeness of the study pool for further investigations was conducted, as the data provided by the company were not suitable for the benefit assessment. This is explained below.

Evidence provided by the company

In its dossier, the company presented the results of the respective single-arm studies on selumetinib. For the ACT best supportive care it presented only data on the annual growth rate of plexiform neurofibromas from the publications it identified on the natural course of the disease. The results section of the dossier did not contain any comparative analyses between selumetinib and the ACT.

Studies on selumetinib

SPRINT study

The pivotal study SPRINT is a single-arm study sponsored by the National Cancer Institute Cancer Therapy Evaluation Program, evaluating selumetinib in children and adolescents aged 2 to 18 years with neurofibromatosis type 1 and inoperable plexiform neurofibromas.

The study was divided into a Phase I dose-finding phase and a subsequent Phase II to characterize the efficacy and safety of selumetinib. Phase II was in turn divided into 2 strata: Stratum 1 comprised a patient population with symptomatic plexiform neurofibromas. In the Stratum 2 population plexiform neurofibromas which do not cause any significant symptoms but merely have the potential to do so were present. For the benefit assessment, the company provided data on Stratum 1 of Phase II. It was clear from the patient characteristics presented in Module 4 A that this stratum comprised exclusively patients aged ≥ 3 years, in accordance with the therapeutic indication to be assessed.

A total of 50 patients were enrolled in Stratum 1 of Phase II at 4 study centres in the United States. The planned follow-up period was 7 years from the start of treatment, or 5 years after discontinuation of the study medication, whichever was longer. At the time of the data cut-off of 31 March 2021 presented in Module 4 A, the median observation period was 41.4 months (Institute's calculation).

Treatment was carried out largely in accordance with the summary of product characteristics (SmPC) for selumetinib [14]. The primary outcome of SPRINT in Stratum 1 of Phase II was the objective response rate. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Studies D1346C00013, D1346C00011, D1346C00015, SPRINKLE and ESR-17-12847

The 5 further studies on selumetinib cited by the company were all single-arm studies, which predominantly enrolled children and adolescents aged between 3 and 18 years with neurofibromatosis type 1 and symptomatic, inoperable plexiform neurofibromas. D1346C00011 and ESR-17-12847 also included adult cohorts; however, these were not relevant to the given research question and were therefore not presented by the company. In each of D1346C00015 and SPRINKLE, only one subpopulation of the paediatric and adolescent

population was considered (D1346C00015: adolescents aged 12 to 18 years; SPRINKLE: children aged 1 to 7 years), meaning that the therapeutic indication under assessment was not fully represented. It was unclear how many patients under the age of 3 outside the therapeutic indication were included in the SPRINKLE study population.

In accordance with the respective study protocols, D1346C00011, D1346C00015 and ESR-17-12847 were also open to patients whose plexiform neurofibromas do not cause significant symptoms, but merely have the potential to do so. However, the study documentation for D1346C00011 indicated that all patients included in the study had symptomatic plexiform neurofibromas at the baseline. However, it was not clear from the available information whether the same also applied to the populations of D1346C00015 and ESR-17-12847.

In total, the analyses presented by the company took into account 118 patients from these 5 studies, 3 of which were conducted exclusively in a single country (D1346C00013: Japan; D1346C00011: China; ESR-17-12847: Korea). The individual populations comprised between 12 (D1346C00013) and 36 (SPRINKLE) patients.

In the studies, an observation period of 2 years or more was planned, with the exception of D1346C00015, in which the planned observation period was shorter than the minimum duration of 24 weeks relevant to the benefit assessment.

In the studies, treatment with selumetinib was largely in compliance with the SmPC [14]. However, contrary to the SmPC, patients in SPRINKLE received selumetinib as granules for at least 3 months instead of the hard capsules usually used, as the dosing regimen, pharmacokinetics and safety profile for this dosage form were to be determined within the scope of the study. However, the study documents indicated that the same dosage regimen applied to the granules as to the hard capsules. Furthermore, the patients in ESR-17-12847 were allocated to different cohorts for the purpose of dose-finding for selumetinib. Some patients were therefore given selumetinib at a dose that differed from that specified in the SmPC. However, in Module 4 A only data from the cohort treated in compliance with the SmPC were presented.

The primary outcomes in these studies were outcomes in the categories of side effects and/or pharmacokinetics. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects. In D1346C00015, harm outcomes were recorded, but no efficacy outcomes were recorded.

Studies on the ACT

On the comparator side, the company presented data from one prospective study (Fisher 2008) and 4 retrospective single-arm studies (Kotch 2023, Nguyen 2012, Nguyen 2013,

Well 2021) on the natural course of the disease to characterize the annual growth rate of plexiform neurofibromas. Given that the ACT determined by the G-BA – best supportive care – is used as a supportive treatment to alleviate symptoms or improve quality of life, and does not result in a reduction in the volume of plexiform neurofibromas, it is reasonable to present data on the natural course of the disease in terms of growth rates of plexiform neurofibromas on the comparator side. No data were presented on the comparator side for any other outcomes.

The company used the results on the range of annual growth rates for plexiform neurofibromas of -13.4% to $+90.0\%$ across all studies to classify the effects of selumetinib. It explained that, in the studies on the comparator side, positive growth rates of plexiform neurofibromas were observed in a large proportion of patients over the course of the disease, and a reduction in volume occurred only very rarely.

This is consistent with other publications which indicate that, whilst a spontaneous reduction in the volume of plexiform neurofibromas is, in principle, possible during the natural course of the disease, it occurs only rarely, particularly in children [11,15,16]. It was also discussed during the 2 oral hearings on the orphan drug procedure for selumetinib that spontaneous remission does not usually occur in the natural course of the disease [17,18]. However, the results presented by the company were subject to uncertainties, which are explained below.

The information on the studies on the natural course of the disease in Module 4 A was based on publications; the company did not provide any study protocols or clinical study reports. Both children and adults with neurofibromatosis type 1 were included, with the exception of the study by Kotch 2023. This study analysed the influence of puberty on the growth of plexiform neurofibromas in children across 3 cohorts (9-year-olds, 11-year-olds and children going through puberty). For the remaining studies, either individual patient data or analyses for the subgroup of children and adolescents were available; consequently, in Module 4 A the company presented the results on the annual growth rate of plexiform neurofibromas for the age group relevant to the therapeutic indication.

At baseline, patients in some studies (Fisher 2008, Kotch 2023, Nguyen 2013) were required to have a plexiform neurofibroma. In contrast, the studies by Nguyen 2012 and Well 2021 were not restricted to the inclusion of patients with plexiform neurofibromas. In Module 4 A, the company stated that it had included only patients with plexiform neurofibromas, as the publications on the studies presented corresponding analyses or individual patient data. However, it was apparent from the publications on the studies that inclusion was possible largely irrespective of the symptoms and operability of plexiform neurofibromas, or, in some cases, insufficient information was available on the relevant criteria. Exceptions to this were the studies by Fisher 2008 and Nguyen 2013. In the case of the Fisher 2008 study, it can be assumed that only symptomatic plexiform neurofibromas were included, as patients with

small plexiform neurofibromas causing no functional impairment or pain were excluded from the study. However, only patients who, based on criteria defined in the study, were at high risk of progression of plexiform neurofibromas were included. This therefore concerned a specific population within the relevant therapeutic indication, for which it remains unclear whether the results can be transferred to the entire therapeutic indication, and it is also questionable whether these patients are sufficiently similar versus the populations in the studies involving selumetinib. Similar uncertainties apply to the study by Nguyen 2013, as only patients with postoperative neurofibromas were included. Overall, based on the information provided by the company for the studies on the ACT it was not possible to determine what proportion of the respective populations had symptomatic and unresectable plexiform neurofibromas at baseline, in line with the therapeutic indication.

A total of 181 patients were included in the studies / the subpopulations presented for the benefit assessment. The individual populations comprised between 8 (study by Well 2008) and 115 (study by Nguyen 2012) patients. The observation period in each case was more than one year. The studies were conducted in the United States (Fisher 2008, Kotch 2023) and in Germany (Nguyen 2012, Nguyen 2013, Well 2021). One notable feature was that the studies by Nguyen 2012, Nguyen 2013 and Well 2021 were conducted at the same university hospital during overlapping periods. Although the patients were recruited on the basis of different criteria, it was not clear from the available publications whether individual patients may have been analysed in more than one study.

Neither the company's dossier nor the publications submitted relating to the studies contained any precise details regarding the care provided to the patients that could be used to verify whether best supportive care was implemented in accordance with the G-BA's specifications. However, at least for the studies by Nguyen 2012, Nguyen 2013 and Well 2021, it was assumed – given that the studies were conducted in Germany – that treatment was predominantly carried out in accordance with the German health care context.

In each of the studies, outcomes relating to the growth rate of plexiform neurofibromas were recorded. Further outcomes in the categories of morbidity, health-related quality of life and side effects were not recorded.

Evidence presented unsuitable

As described, the company did not provide any comparative analyses of selumetinib and the ACT in its dossier. It justified this on the grounds that a comparison using the propensity score method submitted in the previous orphan drug procedure was not accepted for the benefit assessment due to differences in the study population [19]. Furthermore, the company stated that, for this benefit assessment, it had planned to carry out a new adjusted comparison versus an external control arm using a propensity score model. However, due to marked

heterogeneity between the patient populations and a high proportion of missing values in relevant confounders, only an insufficient degree of overlap was achieved. The company's approach is comprehensible. The following section describes the limitations of the studies presented on selumetinib and on the ACT, and explains why comparability was limited.

Studies on selumetinib

The patient populations in SPRINT (Phase II Stratum 1), D1346C00013 and D1346C00011 largely corresponded to the therapeutic indication under assessment; however, as the studies were conducted exclusively in the United States and Asia, there were uncertainties regarding the transferability of the study results to the German health care context.

For D1346C00015, ESR-17-12847 and SPRINKLE, however, as described, it was unclear whether, and if so to what extent, patients outside the relevant therapeutic indication were included. Furthermore, D1346C00015 had a very short observation period, falling short of the minimum study duration of 24 weeks. Furthermore, due to the age restrictions, D1346C00015 and SPRINKLE represented only a subpopulation of the therapeutic indication. Overall, D1346C00015, SPRINKLE and ESR-17-12847 were therefore not suitable for the benefit assessment.

Studies on the ACT

As no study protocols or clinical study reports were available for the studies on the ACT, the dossier lacked important information on how the studies were conducted and, in particular, on the baseline characteristics of the study populations – such as characteristics of the plexiform neurofibromas – which would be necessary to assess the relevance of the studies. Overall, the comparability with the studies on selumetinib was insufficient / due to a lack of information, the comparability could not be adequately assessed. There were further limitations relating to the fact that, in some studies, only a subpopulation of the therapeutic indication under assessment was analysed, and due to the lack of information on the use of best supportive care.

Irrespective of the aspects mentioned regarding the study populations and the associated questions in terms of similarity and transferability, the company only reported results relating to the annual growth rates of plexiform neurofibromas from the studies on the ACT. As described in the following sections, outcomes that only consider a volume change to plexiform neurofibromas are not regarded as patient-relevant. Overall, it was therefore not possible to carry out the comprehensive assessment required as part of the benefit assessment, taking into account data on outcomes relating to the morbidity, health-related quality of life and side effects categories. Consequently, the studies / subpopulations within these studies assessed by the company were not suitable for the benefit assessment.

Summary

As described, the company merely provided descriptive presentations of the results from the single-arm studies on selumetinib in the dossier; the results section of the dossier did not contain any effect estimates for comparison with the ACT. On the comparator side, the company only presented annual growth rates of plexiform neurofibromas which it had extracted, which enable the classification of the effects of selumetinib.

Overall, therefore, no comparative evidence suitable for the benefit assessment of selumetinib versus the ACT was available. Furthermore, there were uncertainties in the publications submitted by the company regarding the characterization of the natural course of the disease. This related in particular to the questionable similarity between the studies on the selumetinib side and those on the comparator side, the inclusion of patients outside the relevant therapeutic indication, the lack of information on the implementation of best supportive care in the studies on the comparator side, as well as the issues of transferability mentioned and the lack of results on patient-relevant outcomes.

Notes on the volume change outcome

In the given therapeutic indication, patients are symptomatic due to their plexiform neurofibromas. 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. As previously described, spontaneous volume reduction is rare in children during the natural course of the disease, and no disease-modifying drug has been available to date.

However, the volume change outcome is not suitable for benefit assessment in the operationalization presented. This is explained below.

To record the outcome volume change in the selumetinib studies (studies with results for this outcome: SPRINT, D1346C00013, D1346C00011, ESR-17-12847), a volumetric magnetic resonance imaging (MRI) analysis was performed on the plexiform neurofibroma selected as the target lesion by the investigator. The target lesion was defined as the most clinically relevant plexiform neurofibroma suitable for volumetric MRI analysis. The assessment was carried out in accordance with the criteria of the Response Evaluation in Neurofibromatosis and Schwannomatosis (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 [20]. Accordingly, the studies on selumetinib recorded the proportion of patients who experienced a $\geq 20\%$ reduction in the volume of the target lesion. In some studies, including the pivotal study SPRINT, volume reductions of 40%, 60% and 80% were also analysed, as was the percentage reduction in volume versus baseline over the course of the study.

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 [20]. 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 [17,18,20]. 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. It should also be noted that, in the given therapeutic indication – particularly in the case of younger children – further growth and, consequently, a further increase in the impairments described are to be expected [21]. 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. However, it was clear from Module 4 A that none of the patients for whom the relevant analyses were submitted achieved a volume reduction of $\geq 80\%$.

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 reasons of reproducibility of the measurement results

[20]; the patient relevance of a change in volume was not taken into account. 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, be recorded when conducting clinical studies [20].

For the benefit assessment, therefore, data showing what an observed reduction in volume actually means for patients would be crucial. In the given context, in which spontaneous volume reduction occurs only very rarely in the natural course of the disease, data on the volume change outcome from single-arm studies can therefore only be taken into account if a reduction in volume is accompanied by a relevant improvement in symptoms and/or quality of life, as measured using a validated instrument. This could be achieved if, in the analysis, reductions in volume were linked to a recording of symptoms and/or health-related quality of life. The company dossier contained results for numerous patient-reported outcomes in these categories. One possible approach, for example, would be to use an analysis as an outcome that, in addition to a reduction in the volume of the target lesion, also incorporates appropriate patient-reported outcomes, thereby allowing conclusions to be reached about possible improvements in symptoms and/or the patients' quality of life associated with the reduction in volume. Consideration would also need to be given to selecting a suitable timepoint at which both recordings of changes in volume and recordings of symptoms or health-related quality of life are available, whilst ensuring that the minimum study duration of 24 weeks is observed. However, such an operationalization was not planned in the studies presented.

Furthermore, an overall assessment would also require suitable data on outcomes relating to side effects.

Results for the outcome volume change under selumetinib are presented in I Appendix B of the full dossier assessment.

I 4 Results on added benefit

No suitable data were available to assess the added benefit of selumetinib compared with the ACT, best supportive care, for the treatment of symptomatic, inoperable plexiform neurofibromas in paediatric patients with neurofibromatosis type 1 aged 3 years and older. There is thus no hint of an added benefit of selumetinib in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of selumetinib in comparison with the ACT is summarized in Table 5.

Table 5: Selumetinib – probability and extent of added benefit

Therapeutic indication	ACT ^a	Probability and extent of added benefit
Treatment of symptomatic, inoperable plexiform neurofibromas in paediatric patients with neurofibromatosis type 1 aged 3 years and older	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 a hint of a considerable added benefit.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the result of the G-BA's assessment conducted in the context of the market launch in 2021 and the reassessment following the expiry of the decision in 2023. In those assessments, the G-BA had determined a non-quantifiable added benefit of selumetinib. However, in the G-BA's assessment the added benefit was considered proven by the marketing authorization, regardless of the underlying data, due to the special situation for orphan drugs.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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