

Selumetinib

(plexiform neurofibromas associated with neurofibromatosis type 1, 1 to < 3 years)

Addendum to Project A26-09
(dossier assessment)¹

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List of abbreviations

Abkürzung	Bedeutung
FLACC	Face, Legs, Activity, Cry, Consolability
G-BA	Gemeinsamer Bundesausschuss
GIC-pNF	Global Impression of Change for Plexiform Neurofibroma-related Pain
GIS-pNF	Global Impression of Severity for Plexiform Neurofibroma-related Pain
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
MRI	magnetic resonance imaging
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SGB	Sozialgesetzbuch

1 Background

On 23 June 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A26-09 (Selumetinib – Benefit assessment according to §35a Social Code Book V) [1].

In its comments [2], the pharmaceutical company (hereinafter referred to as ‘the company’) presented analyses on the single-arm SPRINKLE study for the data cut of 16 December 2025. Analyses relating to this data cut were not yet available in the dossier [3]. The G-BA commissioned IQWiG with the following assessment of the analyses submitted by the company under consideration of the information provided in the dossier:

- SPRINKLE study: second data cut of 16 December 2025; for the outcome ‘volume change of the target lesion’, the operationalization to be used was the best percentage volume reduction achieved

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

2 Assessment

In its dossier [3], the company used the single-arm approval study SPRINKLE to derive an added benefit. The SPRINKLE study [4-8] is an ongoing study with selumetinib in children aged ≥ 1 to < 7 years with symptomatic, inoperable plexiform neurofibromas associated with neurofibromatosis type 1. The study comprises a treatment phase followed by a long-term safety follow-up. During the treatment phase, patients are treated with selumetinib for 25 cycles, with each cycle lasting 28 days. A total of 39 children from 7 different countries were included in the study, 36 of whom began treatment with selumetinib. Of these 36 patients, 13 were aged between 1 and < 3 years, in line with the therapeutic indication under assessment. Treatment with selumetinib was in compliance with the Summary of Product Characteristics (SmPC) [9,10]. For a detailed study description, see benefit assessment A26-09 [1].

In addition to the SPRINKLE study, the company also aims to transfer the study results from source populations with older age groups (children aged 3 years and older and adolescents; adults) to the target population relevant for the benefit assessment (children aged 1 to < 3 years).

As described in the dossier assessment, the single-arm SPRINKLE study does not allow any conclusions on the added benefit, as comparative data against the appropriate comparator therapy (ACT) are lacking. Furthermore, it is not possible in the present situation to transfer study results from older age groups to draw conclusions on added benefit in this therapeutic indication (for the reasoning, see Benefit Assessment A26-09 [1]).

No analyses on efficacy outcomes were carried out at the this first data cut of 8 April 2024 or the SPRINKLE study available in the dossier. For the SPRINKLE study, the company's dossier therefore only contains results on mortality and outcomes in the side effects category. In its comments, the company presented results from the SPRINKLE study at the data cut of 16 December 2025. This data cut was conducted after all patients had been given the opportunity to complete 25 treatment cycles, and also includes data on outcomes of morbidity and health-related quality of life.

As commissioned, the results of the SPRINKLE study at the data cut of 16 December 2025 presented in the comments are set out below and categorised as necessary. This will be limited to the age group of 1- to < 3 years old, which is relevant to this benefit assessment.

Patient characteristics

The patient characteristics of the subpopulation of children aged 1 to < 3 years in the SPRINKLE study are shown in Table 1.

Table 1: Characteristics of the study populations in the single-arm SPRINKLE study, subpopulation of 1 to < 3-year-olds (multipage table)

Study characteristic category	Selumetinib N = 13
SPRINKLE	
Age [years], mean (SD)	1.5 (0.5)
Sex [F/M], %	54/46
Geographical region, n (%)	
Europe	10 (77 ^a)
United States	2 (15 ^a)
Japan	1 (8 ^a)
Disease duration [months]	
Time since diagnosis of neurofibromatosis type 1, [years], mean (SD)	13.8 (11.1)
Time since diagnosis of inoperable plexiform neurofibromas, mean (SD)	8.2 (10.7)
Reasons for the inoperability of plexiform neurofibromas, n (%)	
Close proximity to vital structures	9 (69)
Invasiveness	9 (69)
Encasement of vital structures	11 (85)
High vascularity	3 (23)
Unacceptable risk associated with general anaesthesia	1 (8)
Other	0 (0)
Volume of the target lesion [mL]	ND
Location of target lesion, n (%)	
Trunk	1 (8)
Trunk/limbs	2 (15)
Limbs	0 (0)
Neck/trunk	1 (8)
Head and neck	5 (38)
Head	4 (31)
Other	0 (0)
Symptoms caused by the target lesion, n (%) ^b	
Any symptoms	13 (100)
Pain	5 (38)
Disfigurements caused by plexiform neurofibromas	7 (54)
Impaired movement	0 (0)
Motor weakness	1 (8)
Loss of vision	1 (8)
Airway obstruction	4 (31)
Dysphagia	1 (8)
Hearing loss	0 (0)

Table 1: Characteristics of the study populations in the single-arm SPRINKLE study, subpopulation of 1 to < 3-year-olds (multipage table)

Study characteristic category	Selumetinib N = 13
Respiratory compromise	1 (8)
Impaired bladder function	1 (8)
Speech disorders	1 (8)
Other symptoms	1 (8)
Lansky performance status, n (%)	
Fully active, normal (100)	11 (85)
Minor limitations in physically demanding activities (90)	0 (0)
Active, but tires more quickly (80)	2 (15)
Treatment discontinuation, n (%)	ND
Study discontinuation, n (%)	ND
a. Institute's calculation. b. Patients may have exhibited ≥ 1 symptom. F: female; M: male; n: number of patients in the subpopulation; n: number of patients in the category; N: number of patients in the subpopulation; ND: no data; SD: standard deviation	

Note on the outcomes presented in the comments

Outcome: change in tumour volume

To record the outcome change in tumour volume in the SPRINKLE study, a volumetric magnetic resonance imaging (MRI) analysis was carried out of 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 [11]. However, in order to assess the results on the outcome volume change, it must be considered that volumetric MRI analysis is, in principle, suitable for determining volume changes in plexiform neurofibromas, but 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.

Notwithstanding these uncertainties, it is unclear to what extent a universal response criterion of a 20% change in volume is relevant to patients. 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. Therefore, data showing what an observed volume reduction actually means for patients would be crucial for a benefit assessment. These data were not available.

The criticisms mentioned above on the outcome tumour volume change apply equally to the outcomes response and progression-free survival presented by the company in its comments, as these are also based on changes in tumour volume.

For a detailed assessment of the outcome change in tumour volume, please refer to dossier assessment A25-146 on neurofibromatosis type 1 in children aged 3 years and older and adolescents [12].

Incomplete results in parent-reported outcomes

In its comments, the company did not present results for all parent-reported outcomes recorded in the SPRINKLE study. The appendix to the comments [8] contains results for two scales relating to the outcome pain (Global Impression of Severity for plexiform neurofibroma-related pain [GIS-pNF] and Global Impression of Change for plexiform neurofibroma-related pain [GIC-pNF]). Both scales record the child's pain, based on the parents' assessment, using a question asked at the start of each cycle. However, no results are available for the Face, Legs, Activity, Cry, Consolability (FLACC) scale used in the study. The FLACC is a tool for assessing the pain intensity in young children based on their behaviour across five categories: facial expressions, leg movements, activity, crying and soothing. Unlike the GIS-pNF and GIC-pNF, which consist of just one question, the FLACC therefore records children's pain in greater detail and more frequently (daily over the seven days prior to each visit), based on the parents' assessment. Notwithstanding the check of the instrument's validity, the data subsequently submitted for the age group of 1 to < 3 years, which is relevant to the present therapeutic indication, therefore contain incomplete results.

This addendum presents the severity of pain, as recorded with the GIS-pNF at baseline and at Cycle 25. The change in pain levels recorded with the GIC-pNF merely reflects the change since the previous visit. As there are no data available for this scale in comparison with baseline, the results are not informative, regardless of the absence of a comparator group. A presentation is therefore not provided.

Results

The results for the outcome change in volume of the target lesion (Table 2 and Figure 1) are presented below in accordance with the G-BA's commission and are categorized as interpretation aid. The results for further outcomes in the category morbidity and health-related quality of life (Table 3), as well as for the outcome categories mortality and side effects (Table 4) are presented thereafter.

Volume change of the target lesion

Table 2: Results (morbidity, volume change of the target lesion) – single-arm SPRINKLE study, subpopulation of 1- to < 3-year-olds

Study outcome category outcome operationalization timepoint	Selumetinib		
	N	volume at baseline (mL) mean (SD) median [Q1; Q3]	percentage change in volume ^a mean (SD) median [Q1; Q3]
SPRINKLE			
Morbidity			
Volume change of the target lesion ^b			
Percentage change from baseline			
At the time the best change was achieved ^c	13	37.84 (40.27) 13.73 [10.04; 65.91]	-9.61 (20.86) -5.44 [-53.6; 33.5]
For Cycle 25	13	37.84 (40.27) 13.73 [10.04; 65.91]	15.20 (47.20) -1.93 [-19.38; 34.66]
	N	Patients with event, n (%)	
A reduction of ≥ 20 % ^d from baseline	13	4 (30.8)	
a. A negative value indicates a reduction, whilst a positive value indicates an increase in volume.			
b. Assessment by an independent centralized review; the target lesion was defined as the most clinically relevant plexiform neurofibroma suitable for volumetric MRI analysis. The assessment was conducted in accordance with the criteria of the REiNS working group.			
c. The best achieved change is the maximum reduction in volume compared with baseline, or the minimum increase in volume if there was no volume reduction.			
d. At any time up to Cycle 25.			
MRI: magnetic resonance imaging; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis; SD: standard deviation			

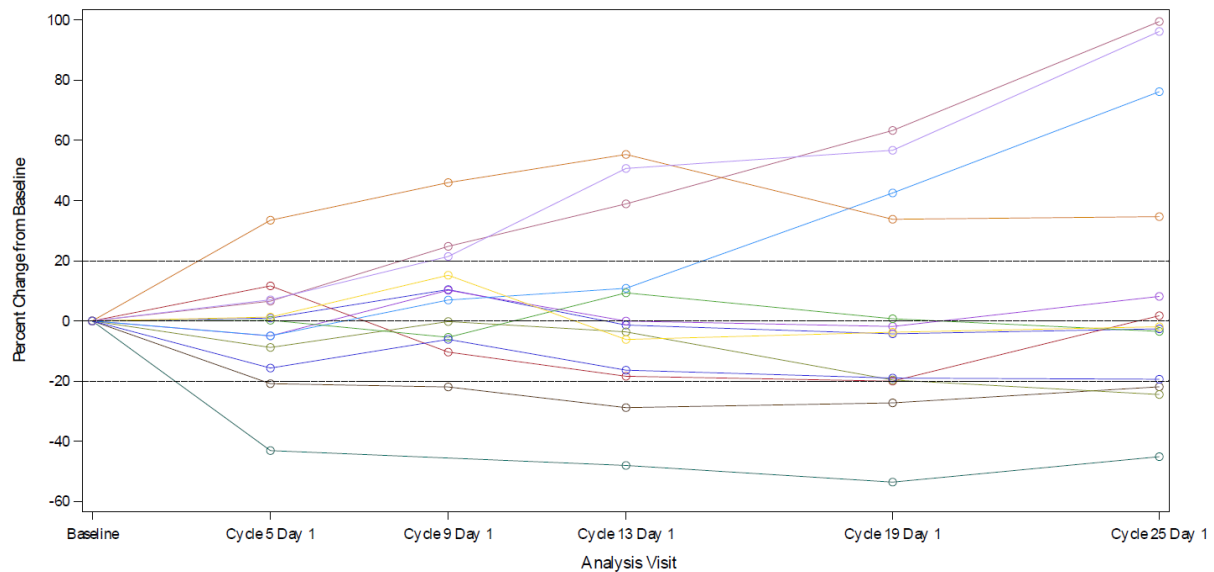


Figure 1: Percentage change in the volume of the target lesion compared with baseline over the course of the study for individual patients – single-arm SPRINKLE study, subpopulation of 1- to < 3-year-olds

Interpretation of the results on the change in the volume of the target lesion

The outcome change in volume of the target lesion in the operationalization ‘best achieved percentage volume change’ indicated according to the study documents – referred to by the company in the comments as the ‘best achieved percentage volume reduction’ – is operationalized as follows: the best achieved percentage volume change was defined as i) the maximum percentage reduction in volume versus baseline, or ii) the minimum percentage increase in volume compared with baseline, if no reduction in volume compared with baseline occurred at any point. As a result of this operationalization, both reductions and increases in volume are included in the analysis.

In the subpopulation of the 1- to < 3-year olds, no volume reduction versus baseline was observed at any point up to Cycle 25 in 3 (23.1%) patients (see Figure 1). This contrasts with the statement made by the company in its comments, according to which, with reference to the study report [7], a reduction in volume was achieved in all patients during the course of the study [2]. Both the study report [7] and the appendix to the comments [8] indeed contain corresponding results, according to which 100% of patients experienced a reduction (‘any reduction’). However, in light of the data shown in Figure 1, according to which three patients never achieved any volume reduction compared with baseline, these figures are not comprehensible. At the end of treatment at Cycle 25, 6 (46.2%) patients were found to have a larger volume and 7 (53.8%) patients a smaller volume compared with baseline (see Figure 1). In this respect, it is misleading in the present situation to speak of the best achieved percentage reduction in volume. This is also shown when considering the best mean or

median percentage change in volume achieved. At the time of the best achieved change – that is, at different points in the course of the study for each individual patient – the mean and median best achieved percentage change in volume was –9.61 and –5.44 respectively (i.e. a mean and median reduction by approx. 10% and 5% respectively) (see Table 2). However, when considering the end of treatment at Cycle 25 for all patients, the mean percentage change in volume was 15.20 (i.e. a mean increase of approx. 15%) and the median one was –1.93 (i.e. a median reduction by approx. 2%).

Overall, the subpopulation of the 1- to < 3-year olds thus presents a very heterogeneous picture of changes in tumour volume, with variations in both directions.

Further outcomes on morbidity and health-related quality of life

Table 3: Results (morbidity, health-related quality of life) – single-arm SPRINKLE study, subpopulation of 1- to < 3-year-olds

Study outcome category outcome	Selumetinib		
	N	number of patients at baseline n (%)	number of patients at Cycle 25 n (%)
SPRINKLE			
Morbidity			
Pain (GIS-pNF ^a)			
No pain	13	9 (69.2)	13 (100)
Mild	13	2 (15.4)	0 (0)
Moderate	13	2 (15.4)	0 (0)
Severe	13	0 (0)	0 (0)
	N	Values at baseline mean (SD)	Change at Cycle 25 LS mean^b (SE)
Health-related quality of life			
PedsQL (parent-reported) ^c			
Total score	13	82.64 (14.71)	5.19 (3.48)
a. Parent-reported scale assessing the severity of pain caused by plexiform neurofibroma over the last 7 days (0: 'none', 1: 'mild', 2: 'moderate', 3: 'severe'). b. Analysis using a mixed-effects model with repeated measures (MMRM). c. PedsQL Infant Scale (age: 13 to 24 months) and PedsQL Generic Core Scale (age: 2 to 4 years), each acute versions with a 7-day recall; higher (increasing) scores indicate a better health-related quality of life (scale range 0 to 100). GIS-pNF: Global Impression of Severity for Plexiform Neurofibroma-related Pain; LS: Least Squares; n: number of patients in the category; N: number of analysed patients; PedsQL: Pediatric Quality of Life Inventory; SD: standard deviation; SE: standard error			

Mortality and adverse events

Table 4: Results (mortality, side effects) – single-arm SPRINKLE study, subpopulation of 1- to < 3-year-olds

Study outcome category outcome	Selumetinib	
	N	patients with event, n (%)
SPRINKLE		
Mortality		
All-cause mortality	13	0 (0)
Side effects		
AEs (supplementary information)	13	13 (100)
SAEs	13	3 (23.1)
Severe AEs ^a	13	6 (46.2)
Discontinuation due to AEs	13	0 (0)
a. Operationalized as CTCAE grade ≥ 3. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; n: number of patients in the category; N: number of analysed patients; SAE: serious adverse event		

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