17 October 2024
EMA/CHMP/478212/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Koselugo

Selumetinib

Procedure no: EMEA/H/C/005244/P46/006

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	19/08/2024	19/08/2024	☐
☐	CHMP Rapporteur Assessment Report	23/09/2024	23/09/2024	☐
☐	CHMP members comments	07/10/2024	07/10/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	10/10/2024	10/10/2024	☐
☒	CHMP adoption of conclusions:	17/10/2024	17/10/2024	☐

Table of contents

1. Introduction

On 3rd of July, the MAH submitted a completed paediatric study for Koselugo, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s)

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Selumetinib, a Selective Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor, in Japanese Paediatric Subjects with Neurofibromatosis Type 1 (NF1) and Inoperable and Symptomatic Plexiform Neurofibromas (PN) (D1346C00013) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study D1346C00013 (Study 13), selumetinib was taken orally in a 10 mg (white) or 25 mg (blue) capsule.

Batch numbers for selumetinib 10 mg: 63337.3/1, 63337.8/1, 63337.14/1

Batch numbers for selumetinib 25 mg: 63337.5/1

As recommended in the SmPC, multiple doses of selumetinib were administered at 25 mg/m^2 BID (every 12 hours) continuously for 28-day cycles (no rest periods between cycles). The dosage was adjusted for changes in Body Surface Area (BSA) and doses were to be rounded to the nearest 5 to 10 mg using a dosing nomogram (**Table 1**)

Table 1. Dosing Nomogram for the Selumetinib PK Study

25 mg/m^2	BSA (m^2)	0.55 to 0.69	0.7 to 0.89	0.9 to 1.09	1.1 to 1.29	1.3 to 1.49	1.5 to 1.69	1.7 to 1.89	≥1.9
	Dose[a] AM (mg)	20	20	25	30	35	40	45	50
	Dose[a] PM (mg)	10	20	25	30	35	40	45	50

[a]Actual dose in mg (capsule sizes 10 and 25 mg) administered BID approximately every 12 hours.
BID = twice daily; BSA = body surface area. PK = pharmacokinetic.

Assessor's comment:

The drug products (10 and 25 mg capsules) used in **Study 13** supporting clinical data in Japanese paediatric patients in this submission are already approved and deemed suitable for the claimed dosing scheme. No complementary biopharmaceutical investigation is needed.

2.3. Clinical aspects

2.3.1. Introduction

In Europe, selumetinib is approved (conditional market authorisation) under the brand name of Koselugo. Two strengths of hard capsules, 10 and 25 mg are available.

Selumetinib is actually used as monotherapy for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

The recommended dose of selumetinib is 25 mg/m^2 individualised based on body surface area (BSA) and taken orally twice daily (BID). Dosing is rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg for BSA ≥ 1.9 m^2). Selumetinib is not recommended in patients with a BSA < 0.55 m^2.

The pharmacokinetic (PK) properties of selumetinib were sufficiently characterized in the initial MAA. Please refer to section 5.2 of the current SmPC.

In the current PAM procedure EMEA/H/C/5244/P46, the Applicant submitted the results of **Study 13**: a Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Selumetinib in Japanese Paediatric subjects with Neurofibromatosis Type 1 (NF1) and Inoperable and Symptomatic Plexiform Neurofibromas (PN)". No change in PK properties is claimed and no change to the product information is proposed within the current PAM submission.

2.3.2. Clinical Pharmacology

2.3.2.1. Methods

Bioanalysis

In **study 13**, selumetinib and its active metabolite N-desmethyl selumetinib in human plasma were quantified in human plasma were quantified using the validated ANAHPP HPLC-MS/MS method. Briefly, calibration, QC and clinical samples (50 µL) were spiked with [$^{13}C_6$] selumetinib and [$^{13}C_6$] N-desmethyl selumetinib as internal standards and using K2-EDTA as anticoagulant. The lower and upper limits of quantification of the method are 2.0 ng/mL and 2000 ng/mL, for selumetinib and 2.00 ng/mL and 500 ng/mL for N-desmethyl selumetinib.

24 samples were reanalysed to test for reproductibility of the method. 100% of the ISR results had a relative difference % within ± 20% for selumetinib and 79.2% for its metabolite.

Study D1346C0013

This was an open label, single arm Phase 1 study designed to evaluate the safety, tolerability, PK and clinical efficacy of selumetinib in Japanese paediatric patients with NF1 and inoperable and symptomatic PN.

Approximately 9 to 12 paediatric patients were planned to be enrolled.

At Cycle 1 Day 1, patients received multiple dose of selumetinib 25 mg/m2 BID (Dose capped at 50 mg for BSA over 1.9) on a continuous schedule (28 days per cycle). PK sampling was performed at Cycle 1 Day 1 and Cycle 2 Day 1 for the assessment of before dosing and until 10-12 hour post dose.

PK samples consisted at Cycle 1 Day 1 of pre-dose, 0.5, 1.5, 3, 6, 10-12h post dose and at Cycle 2 Day 1 of pre-dose, 0.5, 1.5, 3, and 6h post dose.

Standard Plasma PK parameters after multiple dose (Cmax, Tmax, AUC, AUCt, CL/F, Vz/F and T1/2) for selumetinib and N-desmethyl selumetinib were calculated using standard non- compartmental (model-independent) analysis methods.

PK results were retrieved from the CSR report with a cut-off date of **16 June 2021**.

2.3.2.2. Results

Overall 12 children aged 7.5 to 18.2 years old (median 13.25 years), with 3/9 male/female were enrolled.

Selumetinib

Geometric mean selumetinib plasma concentration-time profiles following multiple oral administration of 25 mg/m2 BID selumetinib at C1D1 and C2D1 are shown in Table 2 and associated PK parameter estimates in Table 3. Table 4 presented the dose normalized Cmax and AUCt at C1D1.

Following multiple oral dose of selumetinib 25 mg/m^2 BID in paediatric Japanese patients, absorption of selumetinib was generally rapid with a median Tmax of 1.5h. For selumetinib, geometric mean Cmax was 869 ng/mL, AUC0-6h 2393 ng.h/mL and Rac Cmax and AUC were 1.1 and 1.3 respectively.

Overall, the PK profile in Japanese paediatric patients appeared to be similar to that observed in a previous study, SPRINT Phase II Stratum 1 (Study D1532C00057; NCT01362803).

Table 2: Geometric mean (gSD) plasma concentration-time profiles of selumetinib at c1D1 and C2D1 following multiple dose (N=12)

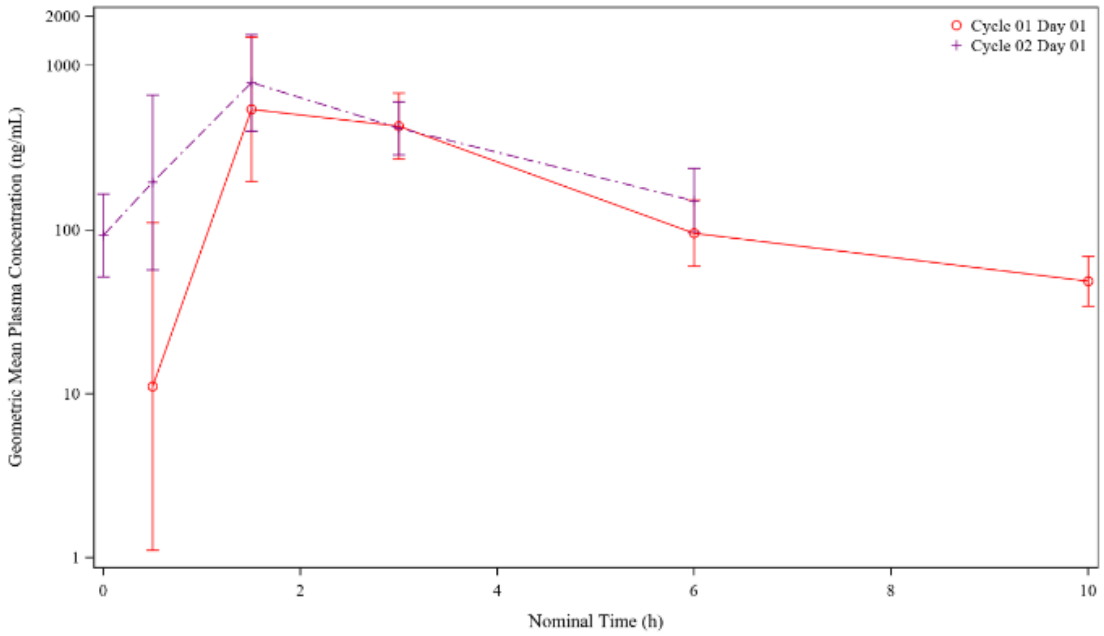


Table 3: Summary of key plasma PK parameters at steady state of selumetinib following multiple dose (N=12)

Parameter (units)	Statistic	Cycle 1 Day 1 (N=12)	Cycle 2 Day 1 (N=11)
C_{max} (ng/mL)	Geomean	783.1	869.4
	gCV%	52.70	53.53
t_{max} (h)	Median	1.49	1.47
	Min-Max	0.50-3.05	0.42-2.87
AUC_{0-t}[a] (ng·h/mL)	Geomean	2224	2395
	gCV%	37.61	40.32
AUC_{0-6} (ng·h/mL)	Geomean	1926	2396
	gCV%	41.64	40.32
AUC_{0-12} (ng·h/mL)	Geomean	2523[b]	NA
	gCV%	24.23	NA
C_{trough} (ng/mL)	Geomean	NA	92.66
	gCV%	NA	63.21
Rac C_{max}	Geomean	NA	1.101
	gCV%	NA	34.30
Rac AUC[c]	Geomean	NA	1.271
	gCV%	NA	17.32

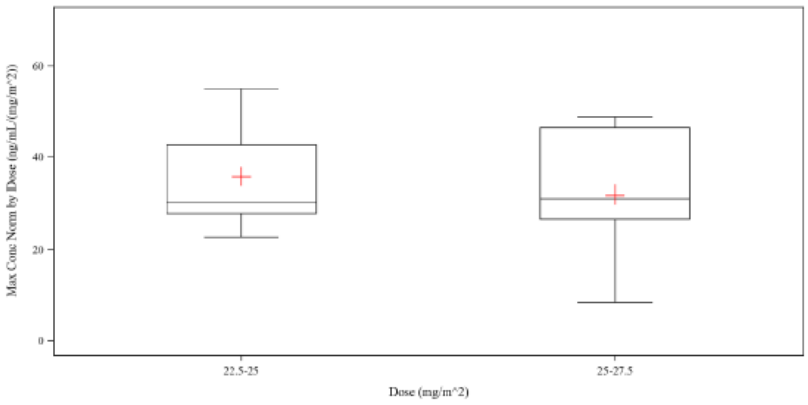
[a] The last sample was 10 to 12 hours post-dose for Cycle 1 Day 1 and 6 hours post-dose for Cycle 2 Day 1.

[b] N=8

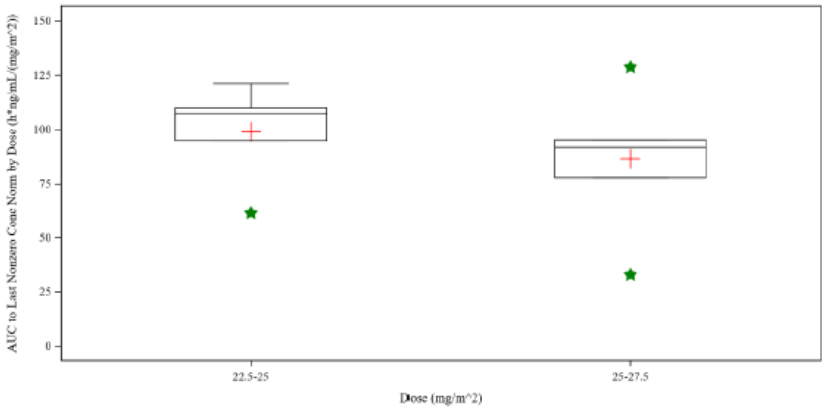
[c] Rac AUC was calculated using AUC_{0-6} for Cycle 1 Day 1 and Cycle 2 Day 1.

Table 4 : Box-plot of selumetinib dose-normalised PK parameters by actual dose group (mg/m²) following single dose

(1) Dose-normalised C_{max}



(2) Dose-normalised AUC_{0-t}



N-desmethyl selumetinib

Conversion to the N-desmethyl metabolite from parent was low. The geometric mean metabolite to parent ratios on Cycle 1 Day 1 and Cycle 2 Day 1 were 7.08% and 4.70% for Cmax and 7.63% and 5.16% for AUC0-t, respectively.

Assessor's comment:

PK results from **Study 13** indicate that**:**

- Compared to exposure PK parameters reported in the SmPC after single dose, Japanese paediatric subject have a similar geomean Cmax (783 vs 731 ng/mL) and a 25% increased of AUC0-12h (2523 vs 2009 ng.h/mL). These results are in line with those reported in the SmPC (Section 5.2, Ethnicity).

The applicant states that selumetinib PK in this Japanese cohort were similar to those observed on the SPRINT study, however no direct comparison was presented.

Since no SmPC updates were performed by the applicant, no questions are raised.

2.3.3. Clinical efficacy/Safety

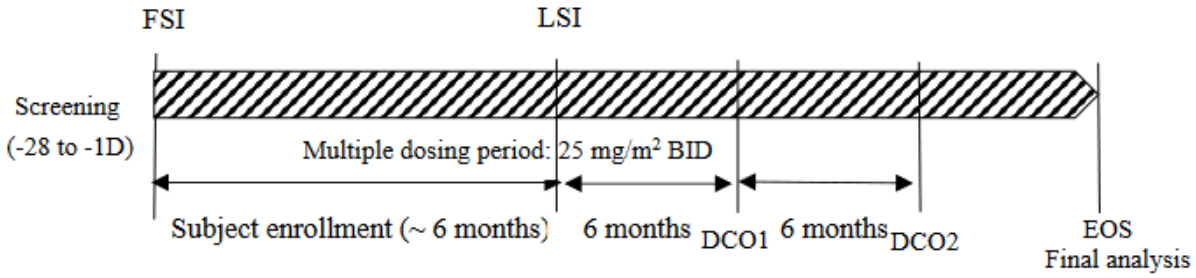
Clinical study number and title

D1346C00013 : A Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of Selumetinib, a Selective Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor, in Japanese Paediatric Subjects with Neurofibromatosis Type 1 (NF1) and Inoperable and Symptomatic Plexiform Neurofibromas (PN)

Description

This was an open label, single arm Phase 1 study designed to evaluate the safety, tolerability, PK, and efficacy of selumetinib in Japanese paediatric subjects with NF1 and inoperable and symptomatic PN.

Table 5 Flow Chart of study Design



BID=twice daily, D=Day, DCO=data cut-off, EOS=end of study, FSI=first subject in, LSI=last subject in.

Methods

Study participants

Main inclusion criteria

Age

Subjects ≥3 years and <18 years of age with a BSA ≥0.55 m^2 at the time of study enrolment who were able to swallow whole capsules.

Disease diagnosis

- Subjects with NF1 and inoperable and symptomatic PN who had PN-related morbidities (symptom and/or complications), as judged by the Investigator.
    - Inoperable PN is defined as PN that cannot be surgically completely remove without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN.
    - The PN had to cause symptoms or complications, such as (but not limited to) head and neck lesions that could compromise the airway or great vessels, paraspinal lesions that could cause myelopathy brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in deformity (eg, orbital

lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.

- Histologic confirmation of tumour was not necessary in the presence of consistent clinical and radiographic findings but was to be considered if malignant degeneration of a PN was clinically suspected.
- A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with connection between the levels or extending laterally along the nerve.
- Subjects must have at least 1 other diagnostic criterion for NF1 (NIH Consensus Development Conference Statement 1988):
    - Six or more café-au-lait macules >5 mm in greatest diameter in pre-pubertal individuals and >15 mm in greatest diameter in post-pubertal individuals.
    - Freckling in the axillary or inguinal regions.
    - Optic glioma.
    - Two or more Lisch nodules (iris hamartomas).
    - A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis.
    - A first-degree relative with NF1.
- Subjects must have at least one measurable typical or nodular PN, defined as a lesion of at least 3 cm measured in one dimension, which could be seen on at least 3 imaging slices and had a reasonably well-defined contour. Subjects who have undergone surgery for resection of a PN were eligible provided the PN was incompletely resected and was measurable. The target PN was defined as the clinically most relevant PN, which had to be amenable to volumetric MRI analysis and classified as either typical or nodular (ie must not be solitary nodular) At least 9 subjects fulfilling the above criteria were to be enrolled and receive treatment. In the event a subject had a PN lesion <3 cm measured in one dimension, the subject could have been permitted entry if the PN was at least 2 cm in one dimension and the subject had to have significant complications and/or symptoms. At most, 3 such subjects could have been enrolled and received treatment. Their eligibilities were to be carefully discussed with the study physician

- Performance status: subjects >16 years of age must have a Karnofsky performance level of ≥70, and children ≤16 years old must have a Lansky performance of ≥70.
- Adequate haematological function defined as absolute neutrophil count ≥1.5×109/L, haemoglobin ≥9g/dL, and platelet count ≥100×109/L.
- Adequate organ function defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2×upper limit of normal (ULN), total bilirubin ≤1.5×ULN except in the case of patients with documented Gilbert's disease (≤2.5×ULN). Estimated creatinine clearance of ≥60 mL/minute.

Main exclusion criteria

- Evidence of malignant peripheral nerve sheath tumour.
- Prior malignancy or other cancer requiring treatment with chemotherapy or radiation therapy.
- A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the patient's safety, interfere with the absorption or metabolism of selumetinib, or put the study outcomes at undue risk.
- Subjects with clinically significant cardiovascular disease as defined by the following:
    - Known inherited coronary disease;
    - Blood pressure (BP) > the 95th percentile for age, height, and gender
    - Acute coronary syndrome within 6 months prior to starting treatment
    - Uncontrolled angina
    - Symptomatic heart failure New York Heart Association Class II to IV,
    - Prior or current cardiomyopathy including but not limited to the following:
    - Known hypertrophic cardiomyopathy.
    - Known arrhythmogenic right ventricular cardiomyopathy.
    - Previous moderate or severe impairment of LVEF <45% on echocardiogram or equivalent on multigated acquisition (MUGA) even if full recovery has occurred.
    - Baseline LVEF below the LLN or <55%
    - Severe valvular heart disease;
    - Current or history of atrial fibrillation ;
    - QT interval corrected by Fridericia's method (QTcF) >450 ms or other factors that increased the risk of QT prolongation.
- Known history of human immunodeficiency virus, serologic status reflecting active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or any uncontrolled active systemic infection
- Subjects with ophthalmological findings/conditions.
- Have had prior treatment with a MEK, Ras or Raf inhibitor (including, but not limited to,vemurafenib).
- Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must be stopped prior to initiation of selumetinib.
- Receiving herbal supplements or medications known to be strong inhibitors or inducers of the cytochrome P450 (CYP)2C19 and CYP3A4 enzymes unless such products can be safely discontinued at least 14 days before the first dose of study medication.
- ***Treatments***

Subjects received selumetinib 25 mg/m2 twice daily (approximately every 12 hours, under fasted conditions) on a continuous schedule for 28-day cycles, with no rest periods between cycles. The dose was based on BSA and rounded to the nearest 5 to 10 mg. The dose of selumetinib was capped at 50 mg when BSA was ≥1.9 m^2. Dosing of selumetinib continued until either PD based on the Investigator's decision or unacceptable drug-related toxicity, whichever occurred first.

Objective(s) Outcomes/endpoints

Primary objective:	**Endpoints**
To assess the safety and tolerability of selumetinib in Japanese paediatric subjects with NF1 and inoperable PN	AEs, clinical safety laboratory assessments, physical examination, vital signs, weight and height, ECG, echocardiography, ophthalmologic assessment, bone growth and Tanner stages.
To characterise the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Japanese paediatric subjects with NF1 and inoperable PN.	PK parameters for selumetinib and N-desmethyl selumetinib were to be derived from following single dose and multiple doses. These included, but were not limited to: AUC,. AUC0-t, Cmax, tmax, $t_{1/2}$.
Secondary objectives:	**Endpoints**
To evaluate the efficacy of selumetinib on NF1-related PN by ICR volumetric MRI analysis in Japanese paediatric subjects with inoperable and symptomatic NF1-related PN.	Tumour response (ORR and DoR) by independent central review per REiNS criteria using volumetric MRI assessment
To evaluate the effect of selumetinib on the PN-related morbidities (symptom and/or complications) by Investigators in Japanese paediatric subjects with inoperable and symptomatic NF1-related PN.	CGIC for PN-related morbidities (symptom and/or complications) from baseline based on the Investigator's judgement
To determine the effect of selumetinib on health-related quality of life in Japanese paediatric subjects with inoperable and symptomatic NF1-related PN	PedsQL (self- and parent-reported).

Sample size

The primary objective was to determine the safety and tolerability of selumetinib. Therefore, the number of subjects was based on the desire to obtain adequate tolerability, safety and PK data while exposing as few subjects as possible to selumetinib.

Nine to 12 Japanese paediatric subjects with NF1 and inoperable and symptomatic PN were eligible to be enrolled in the study. At least nine of these subjects had to have at least one measurable typical or nodular PN in principle, defined as a lesion of at least 3 cm measured in one dimension. Up to 3 additional subjects could have been enrolled if they had a PN lesion of less than 3 cm but at least 2 cm measured in one dimension and had significant complications and/or symptoms

Randomisation and blinding (masking)

Not applicable

Statistical Methods

There is no formal statistical hypothesis testing on this study.

Descriptive statistics were used for all variables, as appropriate. Continuous variables were summarised by the number of observations, mean, standard deviation, median, minimum, and maximum. For log-transformed data it was more appropriate to present geometric mean, coefficient of variation, median, minimum, and maximum. Categorical variables were summarised by frequency counts and percentages for each category.

Results

Participant flow

Table 6 Subject disposition (Enrolled set - All data)

	Number (%) of subjects (N=12)
Subjects enrolled [a]	12 (100.0)
Safety analysis set [b]	12 (100.0)
Subjects who did not receive treatment	0
Subjects not willing to continue study	0
Disease progression before treatment	0
Other	0
Subjects ongoing study treatment at data cut-off [c]	12 (100.0)
Subjects who discontinued treatment [c]	0
Subject decision	0
Adverse event	0
Severe non-compliance to protocol	0
Condition under investigation worsened	0
Subject lost to follow-up	0
Completed	0
Investigator decision	0
Pregnancy	0
Study terminated by Sponsor	0
Death	0
Consent withdrawal	0
Other	0
Subjects ongoing study	12 (100.0)
Subjects who terminated study [d]	0
Completed	0
Pregnancy	0
Death	0
Adverse Event	0
Subject lost to follow-up	0
Physician decision	0
Study terminated by Sponsor	0
Technical problems	0
Withdrawal by subject	0
Other	0

a informed consent received.
b Safety analysis set - all subjects allocated to treatment who received any amount of study treatment.
c Percentages are calculated from number of subjects who received treatmen
d Percentages are calculated from number of subjects enrolled.
Note: This output uses all data available until the date of final data cut-off.
N=Total number of subject

Recruitment

Data presented in this CSR is as of final DCO (23 December 2022). The first subject was enrolled on 31 August 2020 and last subject was enrolled on 23 December 2020.

Baseline data

Subjects were mostly female (9 out of 12, 75.0%), with median age of 13.25 years (range 7.5 to 18.2 years) (Table 12). Median values for height, weight, and BSA were 142.40 cm, 34.0 kg, and 1.170 m^2

Table 7 Demographic characteristics

Demographic characteristic		(N=12)
Age (years)	n	12
	Mean	12.62
	SD	3.146
	Median	13.25
	Min	7.5
	Max	18.2
Sex n (%)	Male	3 (25.0)
	Female	9 (75.0)
	Total	12 (100.0)
Race n (%)	Asian	12 (100.0)
Ethnic group n (%)	Not Hispanic or Latino	12 (100.0)
Ethnic population n (%)	Japanese	12 (100.0)
Height (cm)	n	12
	Mean	139.81
	SD	13.185
	Median	142.40
	Min	117.4
	Max	156.8
Weight (kg)	n	12
	Mean	35.00
	SD	11.774
	Median	34.00
	Min	20.7
	Max	58.9
Body Surface Area (m^2)	n	12
	Mean	1.159
	SD	0.2412
	Median	1.170
	Min	0.82
	Max	1.59

Note: This output uses all data available until the Cycle 7 Day 1 visit for each individual subject.
Percentages are calculated based on the number of subjects with data (Total row).
Max=Maximum, Min=minimum, N=number of subjects in treatment group, n=number of subjects included in analysis, SD=standard deviation.

The median time from diagnosis of NF1 to start of selumetinib treatment was 9.3 years. All subjects had measurable PN. The target PN volume ranged from 17.6 to 3089.9 mL. About half of the subjects had some restrictions in physically strenuous activity (Performance Status score from 70 to 90) at baseline

Table 8 Disease characteristics at baseline (Safety analysis set)

System organ class/ Preferred term		(N=12)
Time from diagnosis of NF1 to start of selumetinib (years)	n	12
	Mean	10.37
	SD	4.052
	Median	9.28
	Min	4.2
	Max	17.9
NF1 diagnostic criteria n[a] (%)	Any café-au-lait macules	12 (100.0)
	Six or more café-au-lait macules	12 (100.0)
	Freckling in axilla or groin	9 (75.0)
	Optic glioma	1 (8.3)
	Two or more Lisch nodules	6 (50.0)
	A distinctive osseous lesion	4 (33.3)
	A first-degree relative with NF1	5 (41.7)
Target PN classification, n[b] (%)	Typical	11 (91.7)
	Nodular	1 (8.3)
	Solitary nodular	0
Target PN location, n[c] (%)	Neck/trunk	4 (33.3)
	Trunk/extremity	0
	Head and neck	1 (8.3)
	Head	2 (16.7)
	Extremity	2 (16.7)
	Body	0
	Trunk	3 (25.0)
	Other	0
Target PN symptoms, n (%)	Any symptoms	12 (100.0)
	Vision loss	0
	Facial motor dysfunction	1 (8.3)
	Auditory loss	1 (8.3)
	Difficulty swallowing	0
	Abnormal speech	2 (16.7)
	Airway obstruction	2 (16.7)
	Respiratory compromise	2 (16.7)
	Bladder dysfunction	0
	Bowel dysfunction	0
	Motor weakness	4 (33.3)
	Decreased range of motion	2 (16.7)
	Sensory deficit	2 (16.7)
	PN-related disfigurement	11 (91.7)
	Pain	7 (58.3)
	Other symptom	0
	Overall morbidity type - airway	2 (16.7)
	Overall morbidity type - bowel/bladder	0
	Overall morbidity type - disfigurement	11 (91.7)
	Overall morbidity type - motor	5 (41.7)
	Overall morbidity type - pain	7 (58.3)
	Overall morbidity type - vision	0
	Overall morbidity type - other	0
Target PN laterality, n (%)	Bilateral	4 (33.3)
	Right	3 (25.0)
	Left	5 (41.7)
Target PN measurability, n (%)	No	0
	Yes	12 (100.0)

Note: This output uses all data available until the Cycle 7 Day 1 visit for each individual subject
a Subjects can have >1 NF1 diagnostic criteria.
b Classification based on imaging.
c Target PN can involve >1 anatomical site.
Max=Maximum, Min=minimum, N=number of subjects in treatment group, n=number of subjects included in analysis, NF1=Neurofibromatosis Type 1, PN=Plexiform Neurofibromas, SD=standard deviation.

Efficacy results

Efficacy was not the primary endpoint in this study.

Objective Response

As of final DCO, 6 subjects (50.0%, 95% confidence interval [CI]: 21.1%, 78.9%) showed objective response (complete response [CR] or confirmed partial response [cPR] as determined by Independent Central Review [ICR] per Response Evaluation in Neurofibromatosis and Schwannomatosis [REiNS] criteria).

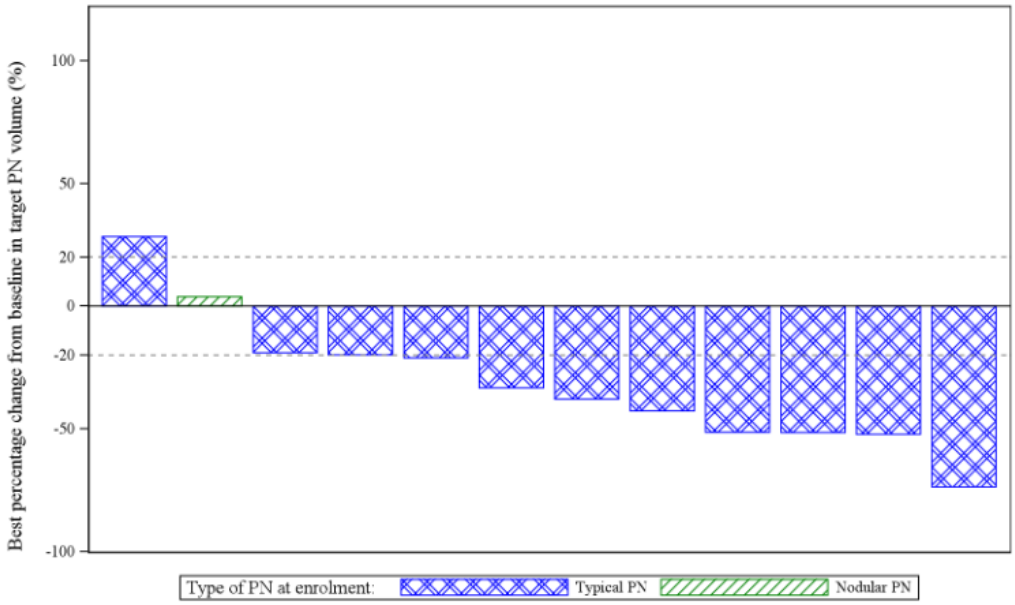
Table 9 Best objective response - based on ICR assessments according to REiNS - subjects with measurable disease at baseline (Safety analysis set - All data)

Response status	Best objective response	Number (%) of subjects (N=12)
Response	Total	6 (50.0)
	Complete response [a]	0
	Partial response [b]	6 (50.0)
Non-response	Total	6 (50.0)
	Stable disease	4 (33.3)
	Unconfirmed partial response [c]	1 (8.3)
	Stable disease	3 (25.0)
	Progression	2 (16.7)
	REiNS progression	2 (16.7)
	Death	0
	Not evaluable	0
	Incomplete post baseline assessments	0

a Response did not require confirmation.
b Response required confirmation within 3 to 6 months.
c Partial response achieved but either no confirmation assessment was performed, or a confirmation assessment was performed but response was not confirmed.
CONFIDENTIAL AND PROPRIETARY 25 of 57 Notes: This output uses all data available until the date of final data cut-off. This table includes subjects who received at least one dose of selumetinib with measurable disease at baseline per ICR.
Subjects in the safety analysis set with no imaging assessments on treatment were to be counted as non-responders.
ICR=Independent central review, N=Total number of subjects, REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis

Target PN Volume

Figure 1 Best Percentage Change from Baseline in Target PN Volume – Waterfall Plot (Safety analysis set – All data)



Duration of Response

As of final DCO, median duration of response (DoR) was not reached. Among 6 subjects who achieved cPR, 1 subject had progressed subsequently. The median total observation duration as of final DCO was 25.8 months (range 24.0 months to 27.2 months) for all 12 evaluable subjects.

Clinical Global Impression of Change responses over time

A total of 11 out of 12 subjects were judged by the Investigators to show an improvement from baseline in their PN-related morbidities at Cycle, while 9 out of 12 subjects reported an improvement from baseline at Cycle 9, Cycle 1, Cycle 17, and Cycle 21.

Table 10 Clinical global impression of change responses over time (Safety analysis set - All data)

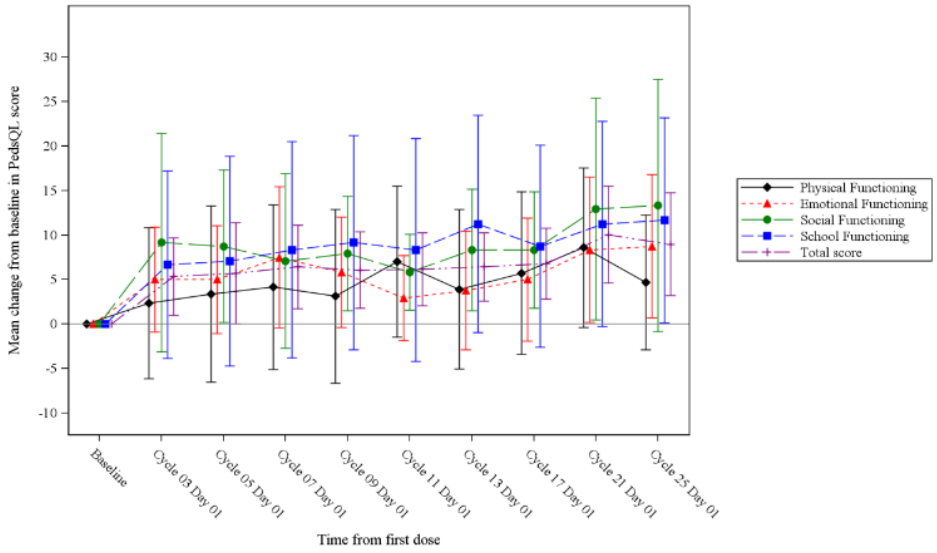
		Number (%) of subjects (N=12)						
Scheduled visit	n	Much better	Moderately better	A little better	About the same	A little worse	Moderately worse	Much worse
Cycle 5 Day 1	12	3 (25.0)	2 (16.7)	6 (50.0)	1 (8.3)	0	0	0
Cycle 9 Day 1	12	2 (16.7)	3 (25.0)	4 (33.3)	3 (25.0)	0	0	0
Cycle 13 Day 1	12	2 (16.7)	3 (25.0)	4 (33.3)	3 (25.0)	0	0	0
Cycle 17 Day 1	12	2 (16.7)	3 (25.0)	4 (33.3)	3 (25.0)	0	0	0
Cycle 21 Day 1	12	2 (16.7)	3 (25.0)	4 (33.3)	3 (25.0)	0	0	0
Cycle 25 Day 1	12	2 (16.7)	2 (16.7)	6 (50.0)	2 (16.7)	0	0	0

Notes: This output uses all data available until the date of final data cut-off.
Clinical Global Impression of Change is the overall evaluation of change of the PN-related morbidities (symptom and/or complications) as assessed by the Investigator.
n=Number of subjects with data at the time point, N=Total number of subjects, PN=Plexiform neurofibromas.

Clinical Outcomes Assessment - Paediatric Quality of Life Inventory

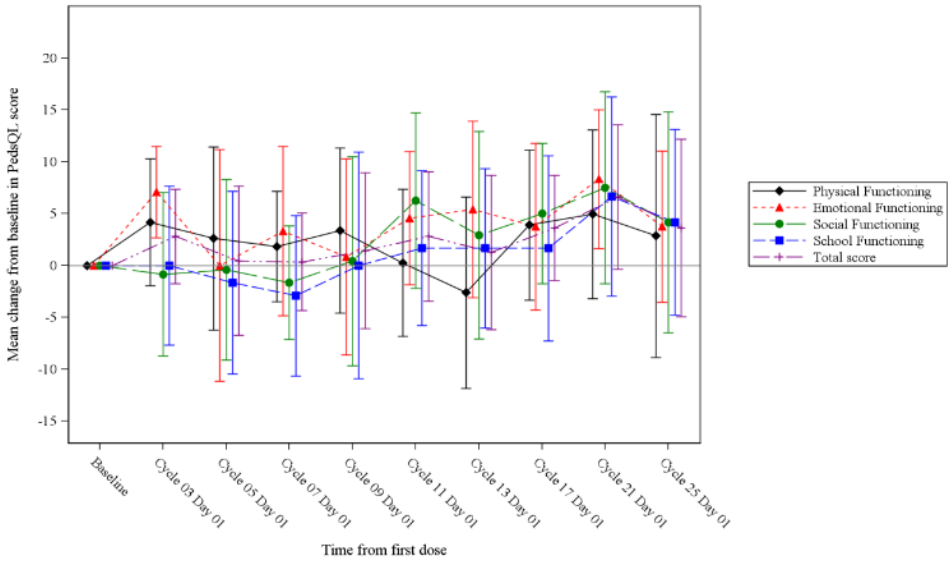
Since all subjects included in Study D1346C00013 were ≥5 years of age and self-reported PedsQL were applicable for all subjects, the primary outcome was the total score of child's self-reported PedsQL.

Figure 2 Mean change from baseline of PedsQL self-report total and domain scores over time - transformed scores (Safety analysis set - All data



Note: This output uses all data available until the date of final data cut-off.
Error bars represent 95% confidence intervals for each respective mean change from baseline.
Higher scores indicate better quality of life, so an increase in score is favourable.
Baseline is defined as the last result obtained prior to the start of study treatment.
PedsQL=Paediatric Quality of Life Inventory

Figure 3Mean change from baseline of PedsQL parent-report total and domain scores over time - transformed scores (Safety analysis set - All data)



scores over time - transformed scores (Safety analysis set - All data)
Note: This output uses all data available until the date of final data cut-off.
The parent-report questionnaire was completed for all age groups.
Error bars represent 95% confidence intervals for each respective mean change from baseline.
Higher scores indicate better quality of life, so an increase in score is favourable.
Baseline is defined as the last result obtained prior to the start of study treatment.
PedsQL=Paediatric Quality of Life Inventory.

Safety results

The median total treatment duration was 25.6 months (range 23.5 to 27.2 months) and the median actual treatment duration was 24.9 months (range 23.0 to 26.5 months).

All 12 subjects experienced at least 1 AE as of cycle 13 Day 1.

Table 7 Number of subjects with adverse events in any category - subject level (Safety analysis set - All data)

AE Category	Number (%) of subjects [a] (N = 12)	Total number of AEs [b] (N = 12)
Any AE	12 (100.0)	164
Any AE possibly related to treatment [c]	11 (91.7)	87
Any AE of CTCAE Grade 3 or higher	2 (16.7)	5
Any AE of CTCAE Grade 3 or higher, possibly related to treatment [c]	2 (16.7)	4
Any AE with outcome = death	0	0
Any AE with outcome = death, possibly related to treatment [c]	0	0
Any SAE (including events with outcome = death)	1 (8.3)	2
Any SAE (including events with outcome = death), possibly related to treatment [c]	1 (8.3)	1
Any AE leading to discontinuation of selumetinib	0	0
Any AE leading to dose reduction of selumetinib	4 (33.3)	6
Any AE leading to dose interruption of selumetinib	4 (33.3)	6
Any AEs of special interest	5 (41.7)	7
Any other significant AEs [d]	NA	NA

Note: This output uses all data available until the date of final data cut-off.

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in >1 category are counted once in each of those categories.

[b] Subjects with multiple PTs in the same category are counted multiple times in that category. Multiple PTs belonging to more than one category are counted multiple times in each of those categories.

[c] As assessed by the Investigator.

[d] Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, are identified and classified as other significant AEs. Includes AEs with an onset date during this period and AEs with an onset date prior to dosing which worsen during this period. Subjects who have an AE leading to discontinuation of treatment after the data cut-off (DCO) date have been reset to the action taken at the DCO date using the dosing information.

AE=Adverse event, CTCAE=Common Terminology Criteria for Adverse Events (version 5.0), N=Total number of subjects, NA=Not applicable, PT=Preferred term, SAE=Serious adverse event.

Medical Dictionary for Regulatory Activities version 25.1.

The most commonly reported (≥10.0% of subjects) AEs were eczema (7 [58.3%] subjects), dermatitis acneiform (6 [50.0%] subjects), paronychia and diarrhoea (5 [41.7%] subjects each), dry skin, stomatitis, and vomiting (4 [33.3%] subjects each).

Table 8 **Most common adverse events (occurring in ≥10% subjects) by system organ class and preferred term (Safety analysis set - All data)**

System organ class/Preferred term	Number (%) of subjects [a] (N = 12)
Subjects with any AE	12 (100.0)
INFECTIONS AND INFESTATIONS	10 (83.3)
Impetigo	3 (25.0)
COVID-19	4 (33.3)
Paronychia	6 (50.0)
Upper respiratory tract infection	2 (16.7)
NERVOUS SYSTEM DISORDERS	4 (33.3)
Headache	4 (33.3)
EYE DISORDERS	4 (33.3)
Periorbital oedema	2 (16.7)
Conjunctivitis	2 (16.7)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (25.0)
Epistaxis	2 (16.7)
GASTROINTESTINAL DISORDERS	11 (91.7)
Abdominal pain	3 (25.0)
Cheilitis	3 (25.0)
Diarrhoea	5 (41.7)
Nausea	3 (25.0)
Stomatitis	4 (33.3)
Vomiting	4 (33.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12 (100.0)
Alopecia	3 (25.0)
Dermatitis acneiform	6 (50.0)
Dry skin	3 (25.0)
Eczema	7 (58.3)
Pruritus	3 (25.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2 (16.7)
Menstruation irregular	2 (16.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (66.7)
Pyrexia	5 (41.7)
Injection site reaction	2 (16.7)
Malaise	2 (16.7)
INVESTIGATIONS	5 (41.7)
Ejection fraction decreased	2 (16.7)
Alanine aminotransferase increased	2 (16.7)
Aspartate aminotransferase increased	3 (25.0)

Note: This output uses all data available until the date of final data cut-off.
[a] Number (%) of subjects with any AEs, sorted by international order for system organ class and alphabetical order for preferred term. Subjects with multiple AEs are counted once for each preferred term. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsen during this period. Percentages are based on the total number of subjects in the treatment group (N).
Medical Dictionary for Regulatory Activities version 25.1.
AE=Adverse event, COVID-19=Coronavirus Disease 2019, N=Total number of subjects.

Among the 12 subjects with AEs, 11 (91.7%) subjects experienced at least 1 AE that was considered to be possibly related to selumetinib, as assessed by the Investigator. The most commonly reported (≥ 10.0% of subjects) AEs considered by the Investigator to be possibly related to selumetinib were eczema (7 [58.3%] subjects), diarrhoea and dermatitis acneiform (5 [41.7%] subjects each), and stomatitis (4 [33.3%] subjects).

Table 9 **Most common (occurring in ≥10% subjects) adverse events possibly related to study drug, by system organ class and preferred term (Safety analysis set - All data)**

System organ class/Preferred term	Number (%) of subjects [a] (N = 12)
Subjects with any possibly related AE [b]	11 (91.7)
INFECTIONS AND INFESTATIONS	7 (58.3)
Paronychia	6 (50.0)
EYE DISORDERS	2 (16.7)
Periorbital oedema	2 (16.7)
GASTROINTESTINAL DISORDERS	9 (75.0)
Cheilitis	3 (25.0)
Diarrhoea	5 (41.7)
Nausea	2 (16.7)
Stomatitis	4 (33.3)
Vomiting	3 (25.0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (91.7)
Alopecia	3 (25.0)
Dermatitis acneiform	6 (50.0)
Eczema	7 (58.3)
Pruritus	2 (16.7)
INVESTIGATIONS	5 (41.7)
Ejection fraction decreased	2 (16.7)
Alanine aminotransferase increased	2 (16.7)
Aspartate aminotransferase increased	3 (25.0)

Notes: This output uses all data available until the date of final data cut-off. Includes only terms with at least 1 possibly related AE. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsen during this period. Percentages are based on the total number of subjects in the treatment group (N).

[a] Number (%) of subjects with any AEs possibly related to study treatment, sorted by international order for system organ class and alphabetical order for preferred term. Subjects with multiple AEs are counted once for each preferred term.

[b] As assessed by the Investigator.

Medical Dictionary for Regulatory Activities version 25.1.

AE=Adverse event, N=Total number of subjects.

No AEs leading to death or AEs leading to treatment discontinuation were reported.

A single subject (8.3%) reported 2 SAEs, both Grade 3 events of paronychia, one of which was assessed as related to study drug. Both SAEs resolved without any action with study drug.

All non-serious AEs were mild or moderate in severity (Common Terminology Criteria for AE Grade 1 or 2) as of Cycle 13 Day 1.

Considering all data up to DCO2, 3 (25.0%) subjects experienced a total of 4 AEs leading to dose interruption (2 events of ejection fraction decreased in 1 subject each that led to dose reduction, and 1 event each of ALT increased and AST increased that resulted in drug interruption in 1 subject each, respectively). The 2 (16.7%) subjects who reported ejection fraction decreased (1 AE each) as of Cycle 13 Day 1 continued selumetinib treatment at a lower dose after dose interruption.

A total of 4 (33.3%) subjects had at 5 AESIs, with a mean (standard deviation [SD]) time to onset of 133.0 days (120.0) as of Cycle 13 Day 1. These included 3 AESIs related to muscular toxicity, including Grade 1 blood creatine phosphokinase increased (1 subject) and myalgia (1 subject with 2 events), and 2 AESIs related to cardiac toxicity, of Grade 2 ejection fraction decreased (1 subject with 1 event, each, as mentioned above). All AESIs were identified during routine investigations, were not associated with any clinical sequelae. All AESIs had resolved as of DCO2, except for 1 AESI of Grade 2 ejection fraction decreased.

Table 11 Number of subjects with adverse events of special interest, by grouped term and preferred term (Safety analysis set – All data)

Specific adverse event of interest	Number (%) of subjects [a] (N = 12)
Subjects with any AESI	5 (41.7)
CARDIAC TOXICITY	3 (25.0)
Ejection fraction decreased	2 (16.7)
Oedema peripheral	1 (8.3)
MUSCULAR TOXICITY	2 (16.7)
Blood creatine phosphokinase increased	1 (8.3)
Myalgia	1 (8.3)

Note: This output uses all data available until the date of final data cut-off.

[a] Number (%) of subjects with any AESIs sorted by alphabetical order for grouped AESI term and preferred term. Subjects with multiple AESIs are counted once for each preferred term. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsen during this period.

Medical Dictionary for Regulatory Activities version 25.1.
AE=Adverse event, AESI=AE of special interest, N=Total number of subjects.

Some laboratory values showed fluctuations during the study (lymphocytes, ALT, AST, and bilirubin). However, no clinically important changes in laboratory values were observed.

2.3.4. Discussion on clinical aspects

The Applicant provided results of a Phase 1 Open Label Study that aimed to assess the Safety, Pharmacokinetics and Clinical Efficacy of Selumetinib in Japanese Paediatric subjects with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN).

There was no primary efficacy endpoint for this study. As of final DCO, BOR was cPR for 6 (50.0%) subjects, unconfirmed PR for 1 (8.3%) subject, stable disease for 3 (25.0%) subjects, and PD for 2 (16.7%) subjects

Assessed by CGIC responses 9 out of 12 subjects were judged by the Investigators to show an improvement from baseline in their PN-related morbidities (symptom and/or complications).

Overall, the efficacy results in the paediatric cohort are coherent with those observed in SPRINT study during the initial marketing authorisation assessment of Koselugo. However, the interpretability of these results is limited due to the small number of subjects included and the open-label design of the study.

Safety data from this study as of DCO2 has demonstrated that selumetinib monotherapy at a dose of 25 mg/m2 BID in Japanese paediatric subjects with NF1 and inoperable PN are consistent with the safety profile of selumetinib as stated under the section 4.4 and 4.8 of Koselugo SmPC and no new safety issues have been identified.

3. Rapporteur's overall conclusion and recommendation

From a clinical Pharmacology perspective, the PK of selumetinib and its metabolite was characterized in a small cohort of 12 paediatric Japanese subjects aged 7.5 to 18.2 years old and results from this study are in line with those reported in Koselugo Section 5.2, Ethnicity.

Based on the data provided by the MAH regarding the results of D1346C00013 study, no new safety or efficacy concerns have been identified as compared to previous studies and experiences in subjects treated with Koselugo.

☒ **Fulfilled:**

No regulatory action required.