17 October 2024
EMA/CHMP/478188/2024
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/P46/005

Note

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

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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	☐

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1. Introduction

On July 2024, 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 study D1346C00011 - A Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Selumetinib (a Selective Mitogen Activated Protein Kinase Kinase [MEK] 1 Inhibitor) in Chinese Paediatric and Adult Patients with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN) a standalone study.

2.2. Information on the pharmaceutical formulation used in the study

In Study **D1346C00011** (Study 11), selumetinib was taken orally in a 10 mg (white) or 25 mg (blue) capsule.

Batch numbers for selumetinib 10 mg: 3164167R, 3187749R

Batch numbers for selumetinib 25 mg: 3174108R, 3185367R

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 11** supporting clinical data in Chinese paediatric and adult 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 11**: a Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Selumetinib in Chinese Paediatric and Adult Patients with Neurofibromatosis Type 1 (NF1) and Inoperable 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 11**, selumetinib and its active metabolite N-desmethyl selumetinib in human plasma were quantified in human plasma, however the bioanalytical report was not provided.

Study D1346C0011

This was an open label, single arm Phase 1 study with two independent cohorts to assess the safety, tolerability, PK and clinical efficacy of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable plexiform NF.

Approximately 16 paediatric and adult patients were planned to be enrolled.

Patients received a single oral dose of selumetinib 25 mg/m2 at Cycle 0 day 1. During the following two days wash-out period, intensive PK samples were collected before and after this first single dose until Cycle 1 Day 1.

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). Intensive PK sampling was performed at Cycle 1 Day 8 for the assessment of AUC12h at steady-state.

PK samples consisted at Cycle 1 Day 0 of pre-dose, 0.5, 1, 1.5, 3, 6, 8, 12, 24 and 30 h post dose and at Cycle 1 Day 8 of pre-dose, 0.5, 1.5, 3, 6, 12h post dose.

Standard Plasma PK parameters after single (Cmax, Tmax, T1/2, AUC, AUC0-12h, AUCt) and multiple dose (Cmaxss, AUC0-12h,ss , and Rac) for selumetinib and N-desmethyl selumetinib were calculated using standard non- compartmental (model-independent) analysis methods.

PK results were retrieved from a CSR report with a cut-off date of **30 January 2022**.

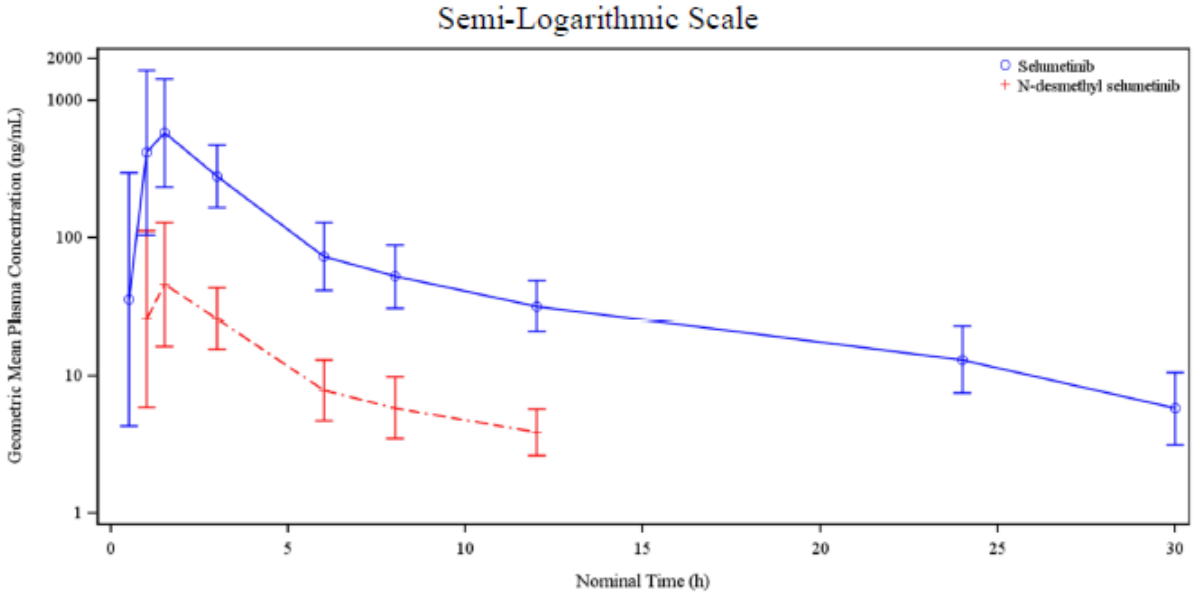
2.3.2.2. Results

Overall 16 children aged 4 to 16 years old (median 11 years), with 9/7 male/female and 16 adults aged 18 to 51 years (median 24.5 years) with 9/7 male/female were enrolled.

Paediatric single dose

Geometric mean selumetinib and N desmethyl selumetinib plasma concentration-time profiles following single oral administration of 25 mg/m^2 selumetinib are shown in **Figure 1** and associated PK parameter estimates in **Table 2**.

Figure 1: Geometric mean (gSD) plasma concentration-time profiles of selumetinib and its metabolite of paediatric cohort following single dose (N=16)



Following single oral dose of selumetinib 25 mg/m^2 in paediatric Chinese patients, absorption of selumetinib was generally rapid with a median Tmax of 1.5h. For selumetinib, geometric mean Cmax was 871 ng/mL, AUC0-12h 2015 ng.h/mL and arithmetic half-life of 7.2 h. For N desmethyl selumetinib, geometric mean Cmax was 64 ng/mL, AUC0-12h 175 ng.h/mL and arithmetic half-life of 7.8 h.

Table 2: Summary of key plasma PK parameters of selumetinib and its metabolite of the paediatric cohort following single dose (N=16)

Parameter	Summary statistic	Selumetinib	N-Desmethyl Selumetinib	Metabolite: Parent ratio
C_{max} (ng/mL)	n	16	16	16
	Geometric mean*	870.9	63.84	0.07331
	gCV (%)*	68.33	72.72	24.46
t_{max} (h)	n	16	16	
	Median	1.5	1.5	
	Min	1.0	1.0	
	Max	3.0	3.0	
AUC_{inf} (h*ng/mL)	n	16	13	
	Geometric mean*	2415	252.2	
	gCV%*	47.36	48.12	
$AUC_{(0-12)}$ (h*ng/mL)	n	16	16	16
	Geometric mean*	2015	175.3	0.08049
	gCV%*	49.97	54.72	26.53
AUC_{last} (h*ng/mL)	n	16	16	
	Geometric mean*	2343	188.6	
	gCV (%)*	47.56	61.72	
λz (1/h)	n	16	13	
	Arithmetic mean	0.10084	0.11113	
	SD	0.023217	0.061623	
$t_{1/2}$λz (h)	n	16	13	
	Arithmetic mean	7.200	7.852	
	SD	1.537	3.378	
CL/F (L/h)	n	16		
	Arithmetic mean	11.81		
	SD	5.171		
Vz/F (L)	n	16		
	Arithmetic mean	122.0		
	SD	53.31		

Paediatric multiple dose

Geometric mean selumetinib and N desmethyl selumetinib plasma concentration-time profiles following multiple oral administration of 25 mg/m2 BID selumetinib are shown in **Figure 2** and associated PK parameter estimates in **Table 3**.

Following multiple oral dose of selumetinib 25 mg/m^2 BID in paediatric Chinese patients, absorption of selumetinib was generally rapid with a median Tmax of 1.5h. For selumetinib, geometric mean Cmax was 1032 ng/mL, AUC0-12h 961 ng.h/mL and Rac Cmax and AUC were 1.3 and 1.5 respectively. For N desmethyl selumetinib, geometric mean Cmax was 76 ng/mL, AUC0-12h 252 ng.h/mL and Rac Cmax and AUC were 1.4 and 1.5 respectively.

Figure 2: Geometric mean (gSD) plasma concentration-time profiles of selumetinib and its metabolite of paediatric cohort following multiple dose (N=16)

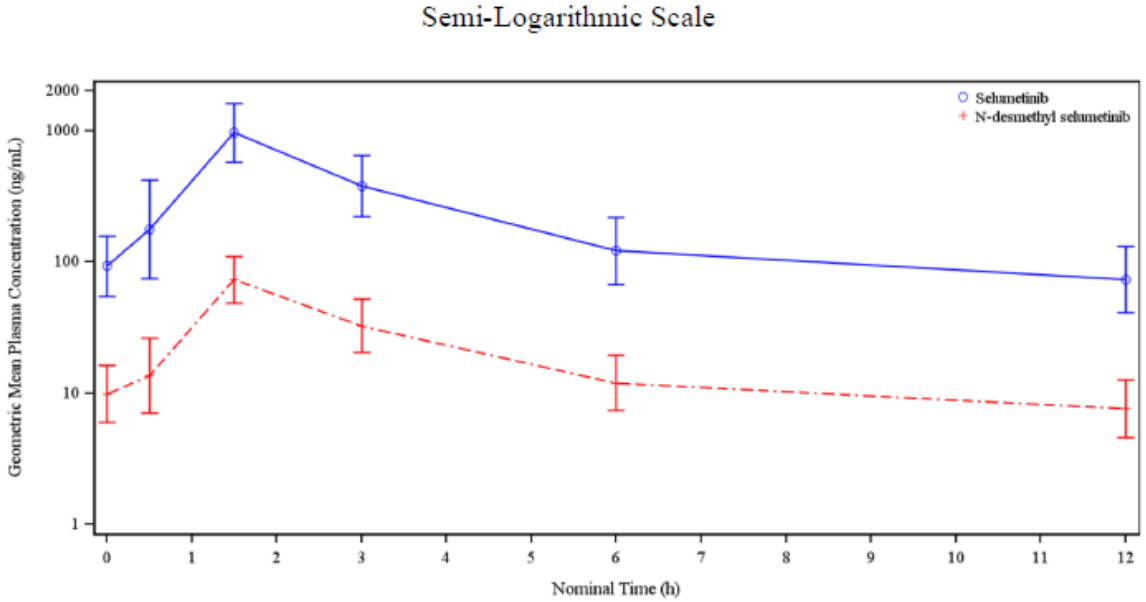


Table 3: Summary of key plasma PK parameters at steady state of selumetinib and its metabolite of the paediatric cohort following multiple dose (N=16)

Parameter	Summary statistic	Selumetinib	N-Desmethyl Selumetinib	Metabolite: Parent ratio
$C_{max,ss}$ (ng/mL)	n	16	16	16
	Geometric mean *	1032	76.50	0.07415
	gCV (%) *	41.28	32.46	24.95
$t_{max,ss}$ (h)	n	16	16	
	Median	1.5	1.5	
	Min	0.5	0.5	
	Max	3.0	3.0	
$AUC_{(0-12),ss}$ (h*ng/mL)	n	16	16	16
	Geometric mean *	2961	251.7	0.08500
	gCV (%)	43.82	36.45	23.46
Rac C_{max}	n	16	16	
	Arithmean	1.289	1.388	
	SD	0.5507	0.8317	
Rac AUC	n	16	16	
	Arithmean	1.511	1.515	
	SD	0.3767	0.5015	
TCP-AUC	n	16	13	
	Arithmean	1.262	1.107	
	SD	0.3294	0.29603	

Overall, the PK profile in Chinese paediatric patients appeared to be similar to that in Western and Japanese paediatric patients from two previous studies, SPRINT Phase II Stratrum I (Study D1532C00057) and Japanese Phase I study (Study D1346C00013), respectively.

Adult single dose

Geometric mean selumetinib and N desmethyl selumetinib plasma concentration-time profiles following single oral administration of 25 mg/m2 selumetinib were provided and not shown here.

Following single oral dose of selumetinib 25 mg/m2 in adult Chinese patients, absorption of selumetinib

Adult multiple dose

Geometric mean selumetinib and N desmethyl selumetinib plasma concentration-time profiles following multiple oral administration of 25 mg/m2 BID selumetinib were provided and not shown here.

Overall, the PK profile in Chinese adult patients appeared to be similar to that in Western and Japanese paediatric patients from two previous studies, SPRINT Phase II Stratrum I (Study D1532C00057) and Japanese Phase I study (Study D1346C00013), respectively.

Assessor's comment:

The applicant states that the observed PK of selumetinib in both adult and paediatric cohorts were similar to those of the SPRINT or Japanese Phase 1 studies (Study D1532C00057, D1346C00013), however no direct comparisons was provided.

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

2.3.3. Clinical efficacy/Safety

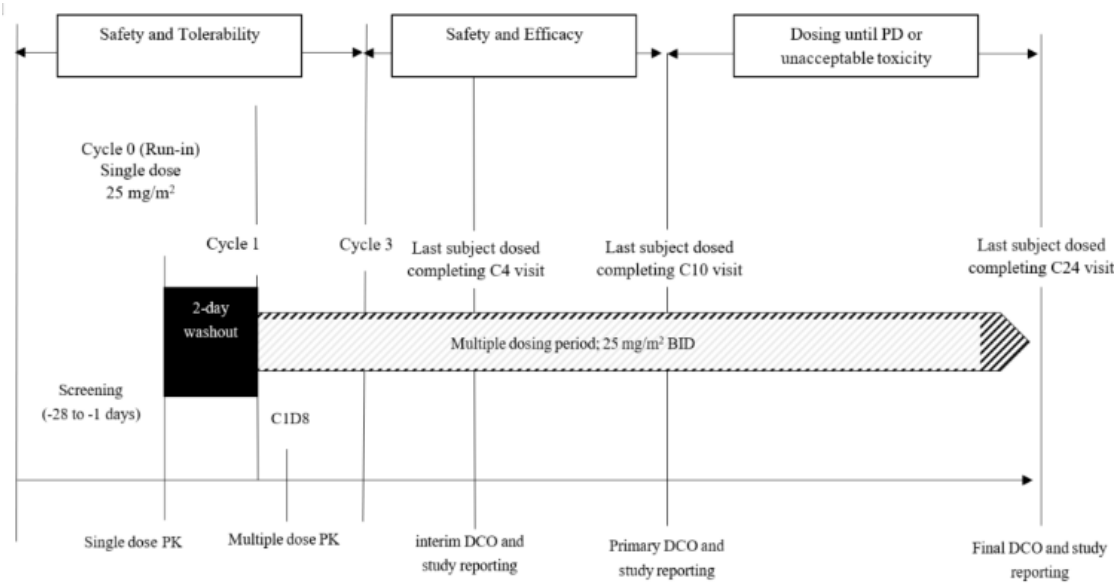
Clinical study number and title

Study D1346C00011: A Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Selumetinib, a Selective Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor, in Chinese Paediatric and Adult Patients with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN).

Description

This is an open label, single-arm Phase I study with 2 independent cohorts to assess the safety, tolerability, PK and clinical efficacy of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN.

Figure 3 Flow Chart of Study Design



BID = twice daily; CnDn = Cycle n Day n; DCO = data cut-off; PD = progressive disease; PK = pharmacokinetics; SRC = Safety Review Committee.
Cohort 1: Paediatric cohort = 16 patients.
Cohort 2: Adult cohort = 16 patients.

Methods

Study participants

Main inclusion criteria

Age

Paediatric cohort: Chinese patients ≥3 years and <18 years of age with a BSA ≥0.55 m2 at the time of study enrolment who were able to swallow whole capsules. There must be a minimum of 6 patients each in the 3 to 11 and 12 to 17 years age groups at the time of enrolment.

Adult cohort: Chinese patients ≥18 years of age at the time of study enrolment who were able to swallow whole capsules

Disease diagnosis

- All study patients must be diagnosed with (i) NF1 per NIH Consensus Development Conference Statement 1988 and (ii) inoperable PN. In addition to PN, patients 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.

A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A histologic confirmation of the 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. Inoperable PN is defined as PN that cannot be completely surgically removed without a risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN.

- Patients' NF1 and inoperable PN required treatment due to actual symptoms or had the potential to develop significant clinical complications, as judged by the investigator, including 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 major deformity (e.g. orbital lesions) or were significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.
- Patients 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. Patients 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).
- Performance status: Patients >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.
- Patients with clinically significant cardiovascular disease as defined by the following:
    - Known inherited coronary disease;
    - Blood pressure (BP) > the 95th percentile for age, height, and genderFor paediatric patients Uncontrolled hypertension (at screening: BP ≥150/95 despite optimal therapy).
    - 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
- Patients 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.

Objective(s) Outcomes/endpoints

Primary objective:	**Endpoints**
To assess the safety and tolerability of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN	Paediatric and adult cohorts: Safety and tolerability were to be evaluated in terms of AEs, clinical safety laboratory assessments, physical examination, vital signs, height/weight, ECG, echocardiogram, ophthalmologic assessment and performance status Paediatric only: Safety and tolerability were also to be evaluated in terms of bone growth and Tanner stages Assessments related to AEs included: • Occurrence/frequency. • Relationship to IP as assessed by investigator. • CTCAE grade. • Seriousness. • Death. • AEs leading to discontinuation of IP. • AEs of special interest.
To characterise the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Chinese paediatric and adult patients 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: After a single dose: • AUC.

	• AUC0-12. • AUC0-t. • Cmax. • tmax. • t1/2. After multiple doses: • AUC0-12,ss. • Cmax,ss. • Rac.
Secondary objectives:	**Endpoints**
To evaluate the clinical efficacy of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN on ORR, DoR, PFS, TTP, and TTR	ORR was defined as the proportion of patients who had a complete response or confirmed partial response (defined as a target PN volume decrease ≥20% compared to baseline, confirmed by a consecutive scan within 3 to 6 months after first response), as determined by the investigator and independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. DoR was defined as the time from the date of first documented response (which was subsequently confirmed) until the date of documented progression or death in the absence of disease progression, as determined by the investigator and independent central review per REiNS criteria. PFS was defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review, or death due to any cause. TTP was defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review. TTR was defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed), as determined by the investigator and independent central review per REiNS criteria.
To evaluate the effect of selumetinib on pain in Chinese paediatric and adult patients with NF1 and inoperable PN	FLACC scale (3 years of age). Faces pain scale - revised (4 to 17 years of age). NRS-11 (adult cohort). PII (adult cohort; self- and parentreported in the paediatric cohort). Pain Medication Survey (self-reported in the adult cohort; parent-reported in the paediatric cohort).
To determine the effect of selumetinib on HRQoL	PedsQL (paediatric cohort; self- and parent-reported). EORTC QLQ-C30 and PlexiQoL (adult cohort)
To determine the effect of selumetinib on physical functioning	PROMIS (upper extremity; self- and parent-reported in the paediatric cohort). PROMIS (mobility; self- and parent reported in the paediatric cohort).

	PROMIS Physical Function - Short Form 8c 7-day (adult cohort).

Sample size

The primary objectives were to evaluate the safety, tolerability and PK of selumetinib. Per the Chinese Phase I PK guideline, at least 8 to 12 patients per cohort were required. To allow for dropouts and non-evaluable cases, 16 patients in each cohort were planned to be enrolled to obtain adequate PK and safety data. There must be a minimum of 6 patients each in the 3 to 11 and 12 to 17 years age groups at the time of enrolment.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

There is no formal hypothesis testing on this study.

Safety data were presented using descriptive statistics by cohort. Evaluations of safety included, but were not limited to, adverse events (AEs), clinical safety laboratory assessments, physical examination, vital signs, bone growth (paediatric cohort only), and Tanner stages (paediatric cohort only).

Pharmacokinetic data were listed and summarised by cohort and timepoint. PK parameters included but were not limited to AUC, Cmax, and tmax. Individual and geometric mean (Gmean) selumetinib and N-desmethyl selumetinib plasma concentrations were presented graphically as appropriate.

Efficacy endpoints, including best overall response (BOR), objective response rate (ORR), target PN volume change, time to response (TOR), duration of response (DoR), time to progression (TTP), and progression free survival (PFS), were presented based on investigator and independent central review (ICR) assessment per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria.

Clinical outcome assessments (COAs) were evaluated and presented for pain, health-related quality of life (HRQoL), physical functioning, patients' global impression of symptom severity (PGIS), and patient's global impression of change (PGIC). The primary analysis of the COAs was based on descriptive statistics. In addition, change from baseline was analysed using a mixed model repeated measures (MMRM) approach.

Results

Participant flow

▪ Paediatric cohort

Table 4 Patient Disposition (All Paediatric Patients)

	Number (%) of patients (N = 20)
Patients enrolled [a]	20 (100)
Screen failure	4 (20.0)
Patients who received treatment	16 (80.0)
Patients who did not receive treatment	4 (20.0)
Safety analysis set	16 (80.0)
Patients ongoing study treatment at DCO [b]	15 (93.8)
Patients who discontinued treatment [b]	1 (6.3)
Disease Progression	1 (6.3)
Patients ongoing study [b]	0
Patients who terminated study [b]	16 (100)
Completed	16 (100)

a Informed consent received.
b Safety analysis set - all patients who received at least 1 dose of selumetinib.
c PK analysis set - all patients who received at least 1 dose of selumetinib and have at least 1 post-dose evaluable concentration-time data point.
d Percentages are calculated from number of patients who received treatment, all other percentages calculated from number enrolled.
N = Number of patients in cohort.
Source: Table 14.1.1 and Table 14.1.3

▪ Adult cohort

Table 5 Patient Disposition (All Paediatric Patients)

	Number (%) of patients (N = 17)
Patients enrolled [a]	17 (100)
Screen failure	1 (5.9)
Patients who received treatment	16 (94.1)
Patients who did not receive treatment	1 (5.9)
Safety analysis set [b]	16 (94.1)
PK analysis set [c]	16 (94.1)
Patients ongoing study treatment at data cut-off [d]	16 (100)
Patients who discontinued treatment [d]	0
Patients ongoing study[d]	16 (100)
Patients who terminated study[d]	0

a Informed consent received.
b Safety analysis set - all patients who received at least 1 dose of selumetinib.
c PK analysis set - all patients who received at least 1 dose of selumetinib and have at least 1 post-dose evaluable concentration-time data point.
d Percentages are calculated from number of patients who received treatment, all other percentages calculated from number enrolled.
N = Number of patients in cohort.

Recruitment

First patient enrolled: 16 December 2020

Last patient last visit: 15 August 2023

▪ Paediatric cohort

A total of 20 paediatric patients (informed consent received) were enrolled in the paediatric cohort, 16 of whom received at least one dose of selumetinib and were included in the Safety Analysis Set. As of this DCO (15 August 2023), 15 patients were still receiving treatment with selumetinib. One patient had discontinued treatment early due to PD; all patients had terminated and completed the study.

▪ Adult cohort

A total of 17 adult patients (informed consent received) were enrolled in the adult cohort, 16 of whom received at least one dose of selumetinib and were included in the Safety Analysis Set.

As of this DCO (15 August 2023), 13 patients were still receiving treatment with selumetinib; 2 discontinued treatment because of 'patient decision' and one discontinued treatment due to 'other' reasons. All patients had terminated the study; 13 patients had completed the study; 2 patients had withdrawn, and one terminated the study due to 'other' reasons.

Baseline data

▪ Paediatric cohort

Demographic characteristics

The median age was 11.0 years old, nine (56.3%) patients were male, Median values for height, weight, and BSA were 134.60 cm, 28.00kg, and 1.095 m2 (range 0.66 to 1.94 m2)

Table 6 Demographic Characteristics of Paediatric Cohort (Safety Analysis Set)

Demographic characteristic	Paediatric (N = 16)	
Age (years)	n	16
	Mean	10.6
	SD	3.77
	Median	11.0
	Min	4
	Max	16
Sex n (%)	Male	9 (56.3)
	Female	7 (43.8)
Race n (%)	Asian	16 (100)
	Total	16 (100)
Ethnic group n (%)	Not Hispanic or Latino	16 (100)
	Total	16 (100)
Ethnic population n (%)	Chinese	16 (100)
	Total	16 (100)

Percentages are calculated based on the number of patients with data (Total row).
Max = Maximum; Min = Minimum; n = Number of patients in category or analysis; N = Number of patients in cohort; SD = Standard deviation.

The disease characteristics at baseline are summarised below;

Table 7 Disease Characteristics at Baseline of Paediatric Cohort (Safety Analysis Set)

	Paediatric (N = 16)	
Lansky Performance status score n (%) [a]	(100) Fully active, normal.	4 (25.0)
	(90) Minor restrictions in physically strenuous activity.	9 (56.3)
	(80) Active, but tires more quickly	2 (12.5)
	(70) Both greater restriction of and less time spent in play activity.	1 (6.3)
NF1 diagnostic criteria n (%) [b]	Any café-au-lait macules	16 (100)
	Six or more cafe-au-lait macules	16 (100)
	Freckling in axilla or groin	16 (100)
	Optic glioma	0
	Two or more Lisch nodules	10 (62.5)
	A distinctive bony lesion	0
	A first-degree relative with NF1	1 (6.3)
Time from diagnosis of NF1 to start of selumetinib (years)	n	16
	Mean	3.8662
	SD	3.90123
	Median	2.7228
	Min	0.424
	Max	14.308
Time from diagnosis of PN to start of selumetinib (years)	n	16
	Mean	3.0746
	SD	4.06040
	Median	1.0897
	Min	0.022
	Max	13.969
Target PN classification, n (%) [c]	Typical	16 (100)
	Nodular	0
	Missing	0
Target PN pain, n (%)	Yes	14 (87.5)
Target PN radiology location, n (%)	Neck/trunk	1 (6.3)

	Trunk/extremity	1 (6.3)
	Head and neck	2 (12.5)
	Head	1 (6.3)
	Extremity	5 (31.3)
	Trunk	3 (18.8)
	Other [d]	3 (18.8)
Target PN volume (mL)	n	16
	Mean	766.67
	SD	772.594
	Median	517.35
	Min	47.6
	Max	2664.4
Target PN overall morbidity type, n (%) [e]	Airway	1 (6.3)
	Bowel / bladder	1 (6.3)
	Disfigurement	5 (31.3)
	Motor	4 (25.0)
	Pain	14 (87.5)
	Vision	0
	Other	16 (100)

a Karnofsky performance status was assessed in patients who were older than 16 years of age, and Lansky performance status was assessed in patients who were 16 years of age or younger. Both the Karnofsky performance status scores and the Lansky performance status scores range from 10 to 100, with higher scores indicating better functioning.
b Patients can have more than one NF1 diagnostic criteria.
c Classification based on imaging.
d Other Target PN radiology locations: 2 patients have "Head neck and Trunk" and 1 has "extremity and Trunk".
e Morbidities are as assessed by the investigator. Patients can have more than one PN-related morbidity.
Max = Maximum. Min = Minimum. n = Number of patients in category or analysis; N = Number of patients in cohort; NA = Not applicable; NC = Not calculated; NF1 = Neurofibromatosis type 1; PN = Plexiform neurofibromas; SD = Standard deviation.

Adult Cohort

Table 8 Demographic characteristics

Demographic characteristic	Adult (N = 16)	
Age (years)	n	16
	Mean	26.1
	SD	8.55
	Median	24.5
	Min	18
	Max	51
Sex n (%)	Male	9 (56.3)
	Female	7 (43.8)
Race n (%)	Asian	16 (100)
	Total	16 (100)
Ethnic group n (%)	Not Hispanic or Latino	16 (100)
	Total	16 (100)
Ethnic population n (%)	Chinese	16 (100)
	Total	16 (100)

Percentages are calculated based on the number of patients with data (Total row).
Max = Maximum; Min = Minimum; n = Number of patients in category or analysis; N = Number of patients in cohort; SD = Standard deviation.

Disease characteristics

The disease characteristics at baseline are summarised

Table 9 Disease Characteristics at Baseline of Adult Cohort (Safety Analysis Set)

		Adult (N = 16)
Karnofsky Performance status score n (%) [a]	(100) Normal, no complaints, no evidence of disease	0
	(90) Able to carry on normal activity. Minor signs or symptoms of disease	10 (62.5)
	(80) Normal activity with effort; some signs or symptoms of disease	5 (31.3)
	(70) Cares for self, unable to carry on normal activity or to do active work	1 (6.3)
NF1 diagnostic criteria n (%) [b]	Any café-au-lait macules	16 (100)
	Six or more cafe-au-lait macules	16 (100)
	Freckling in axilla or groin	15 (93.8)
	Optic glioma	0
	Two or more Lisch nodules	12 (75.0)
	A distinctive bony lesion	4 (25.0)
	A first-degree relative with NF1	8 (50.0)
Time from diagnosis of NF1 to start of selumetinib (years)	n	16
	Mean	7.9225
	SD	9.61043
	Median	4.0575
	Min	0.063
	Max	34.513
Time from diagnosis of PN to start of selumetinib (years)	n	16
	Mean	3.2796
	SD	4.76894
	Median	1.4415
	Min	0.060
	Max	14.513
Target PN classification, n (%) [c]	Typical	13 (81.3)
	Nodular	3 (18.8)
	Missing	0
Target PN pain, n (%)	Yes	4 (25.0)
Target PN radiology location, n (%)	Neck/trunk	0
	Trunk/extremity	0
	Head and neck	1 (6.3)
	Head	4 (25.0)
	Extremity	6 (37.5)
	Trunk	5 (31.3)
	Other	0
Target PN volume (mL)	n	16
	Mean	1434.59
	SD	1942.859
	Median	691.70

	Min	46.2
	Max	7746.3
Target PN overall morbidity type, n (%) [d]	Airway	0
	Bowel / bladder	0
	Disfigurement	2 (12.5)
	Motor	4 (25.0)
	Pain	4 (25.0)
	Vision	2 (12.5)
	Other	4 (25.0)

Karnofsky performance status was assessed in patients who were older than 16 years of age, and Lansky performance status was assessed in patients who were 16 years of age or younger. Both the Karnofsky performance status scores and the Lansky performance status scores range from 10 to 100, with higher scores indicating better functioning.
b Patients can have more than one NF1 diagnostic criteria.
c Classification based on imaging.
d Morbidities are assessed by the investigator. Patients can have more than one PN-related morbidity.
Max = Maximum; Min = Minimum; n = Number of patients in category or analysis; N = Number of patients in cohort; NF1 = Neurofibromatosis type; PN = Plexiform neurofibromas 1; SD = Standard deviation.

Efficacy results

▪ Paediatric cohort

Efficacy endpoints were evaluated as a secondary objective.

Objective Response Rate

As of this DCO, the ORR based on investigator assessment was 81.3% (13/16 patients; 95% CI: 54.4%, 96.0%). The ORR based on ICR assessment was 62.5% (10 out of 16 patients; 95% CI: 35.4%, 84.8%). See Table 10

Table 10 Best Overall Response of Paediatric Cohort, Based on Investigator/ICR Assessments According to REiNS (Safety Analysis Set)

	Number (%) of patients (N = 16)	
	Investigator assessment	**ICR assessment**
Best overall response		
Complete response	0	0
Confirmed partial response [a]	13 (81.3)	10 (62.5)
Unconfirmed partial response [b]	2 (12.5)	1 (6.3)
Stable disease [c]	1 (6.3)	4 (25.0)
REiNS progression [d]	0	1 (6.3)
Not evaluable	0	0
Objective response rate [e]	13 (81.3)	10 (62.5)
95% CI [f]	54.4, 96.0	35.4, 84.8

a Partial response is a decrease in volume of the target PN by 20% or more compared to baseline, and a response of non-progressive disease in the non-target PN, and no new lesions. It is considered unconfirmed at the first detection, confirmed when observed again within 3 to 6 months.
b Partial response achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.

c Insufficient volume change in either target or non-target PN from baseline to qualify for either partial response or progressive disease, and no new lesions observed.
d At least one of: Increase in the volume of the target PN by 20% or more compared to baseline or the time of best response (maximal tumour shrinkage) after documenting a partial response; increase in the volume of the non-target PN by 20% or more compared to baseline; appearance of a new PN.
e Includes patients with a complete response or confirmed partial response as determined by investigator/ICR per REiNS criteria.
f 2-sided exact 95% CI calculated using the Clopper Pearson method. CI = Confidence interval; ICR = Independent central review; REiNS = Response evaluation in Neurofibromatosis and Schwannomatosis; N = Number of patients in cohort; PN = Plexiform neurofibromas

The concordance rate regarding the BOR assessed by investigator and ICR was 68.75% (11/16.

Target PN Volume Changes

All 16 patients had completed at least 1 post-baseline tumour assessment by interim DCO and were included in the summary of change in target PN volume from baseline (see Table 11) and had the chance to complete the Cycle 24 assessment.

Based on investigator assessment, by the end of Cycle 24, the mean (SDev) percentage change in target PN volume from baseline was -41.38% (13.53%).

Based on ICR assessment, by the end of Cycle 24, the mean (SDev) percentage change in target PN volume from baseline was -27.15% (18.3%).

Table 11 Target PN Volume of Paediatric Cohort, Absolute and Percentage Change from Baseline, Based on Investigator/ICR Assessment according to REiNS (Safety Analysis Set)

		Change from baseline (mL)						% Change from baseline				
	Time point	n	Mean	SDev	Median	Min	Max	Mean	SDev	Median	Min	Max
Investigator assessment (N = 16)	Cycle 4, Day 28	16	-158.85	187.601	-119.90	-640.3	61.6	-22.44	12.274	-21.93	-42.7	7.4
	Cycle 8, Day 28	8	-79.54	70.353	-72.60	-194.5	-1.4	-21.40	11.821	-23.88	-38.6	-0.3
	Cycle 12, Day 28	16	-253.29	286.238	-187.75	-943.8	47.2	-32.57	17.181	-37.82	-58.2	10.1
	Cycle 16, Day 28	12	-330.22	353.719	-173.90	-1129.1	-10.9	-39.15	14.614	-40.52	-60.6	-16.9
	Cycle 20, Day 28	16	-280.64	334.547	-179.10	-1215.6	50.6	-30.02	33.690	-43.31	-53.5	80.0
	Cycle 24, Day 28	14	-327.80	332.410	-221.80	-1150.4	-36.4	-41.38	13.527	-45.67	-61.2	-18.3
	Cycle 30, Day 28	5	-107.44	121.873	-86.90	-278.1	39.1	-26.63	22.845	-29.11	-52.0	8.4
ICR assessment (N = 16)	Cycle 4, Day 28	16	-78.12	135.944	-24.46	-405.9	107.8	-12.86	17.993	-15.50	-45.1	22.5
	Cycle 8, Day 28	11	-61.50	100.766	-49.73	-314.0	59.6	-14.52	16.672	-8.10	-43.3	2.8
	Cycle 12, Day 28	16	-152.24	211.487	-89.46	-738.3	52.8	-20.24	24.373	-25.65	-53.9	30.1
	Cycle 16, Day 28	13	-181.12	237.082	-118.33	-745.5	84.0	-19.89	29.349	-23.70	-63.7	47.9
	Cycle 20, Day 28	16	-134.86	225.089	-84.21	-712.2	170.4	-12.73	40.585	-25.65	-61.7	97.2
	Cycle 24, Day 28	14	-176.67	229.158	-109.28	-671.6	144.5	-27.15	18.299	-29.25	-56.5	17.3
	Cycle 30, Day 28	5	-23.53	173.330	-90.36	-141.7	278.3	5.04	87.424	-26.70	-56.6	158.8

A negative change denotes a reduction in PN volume.
Only assessments closest to the protocol scheduled visit day are selected for this summary, therefore unscheduled visits may be excluded. n is the number of patients with a recorded size at baseline and given timepoint.
Max = Maximum; Min = Minimum; N = Number of patients in cohort; PN = Plexiform Neurofibromas; SD = Standard deviation

Duration of response and time to response

Based on investigator assessment, 13 patients reached cPR, the median TTR was 3.7 (95% CI: 3.55, 7.39) months, and the median DoR was not reached.

As of this DCO, 11 patients were still in response at the DCO. The shortest DoR was 8.7 months, and the longest DoR was 20.1 months. 3 patients with cPR had PD based on the REiNS Criteria or death.

Based on ICR assessment, 10 patients reached cPR, the median TTR was 8.7 (95% CI: 3.55, 9.30) months, and the median DoR was not reached. As of this DCO, 8 patients were still in response. The

shortest DoR was 5.3 months, and the longest DoR was 23.7 month. 2 patients with cPR had PD based on the REiNS Criteria or death.

Progression-free survival

Based on investigator assessment, 5 patients (31.3%) had PD based on the REiNS Criteria, and the median PFS was not reached. The median follow-up time was 22.01 months (range: 11.1 to 27.4). The investigator-assessed PFS rate at 24 cycles was 75.0% (95% CI: 46.34, 89.80).

Based on ICR assessment, 6 patients (37.5%) had PD documented based on the REiNS Criteria, the median PFS was not reached. The median (range) follow-up time was 22.00 (3.7-27.4) months. The ICR-assessed PFS rate at 24 cycles was 62.5% (95% CI: 34.86, 81.09).

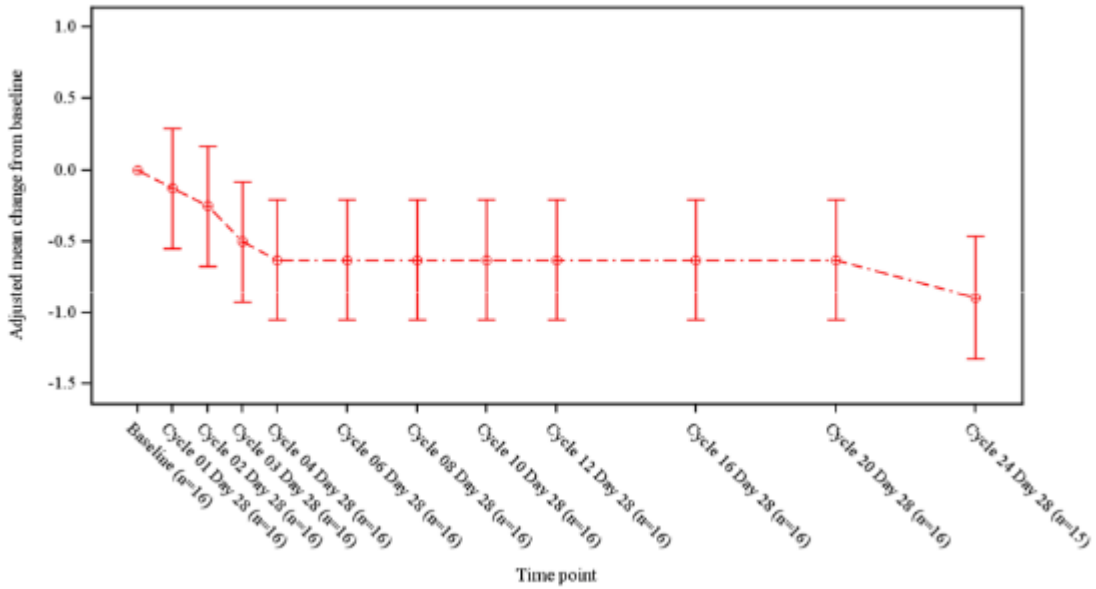
Time to progression

As of this DCO, based on investigator assessment or ICR assessment, the median TTP was not reached

Pain assessment

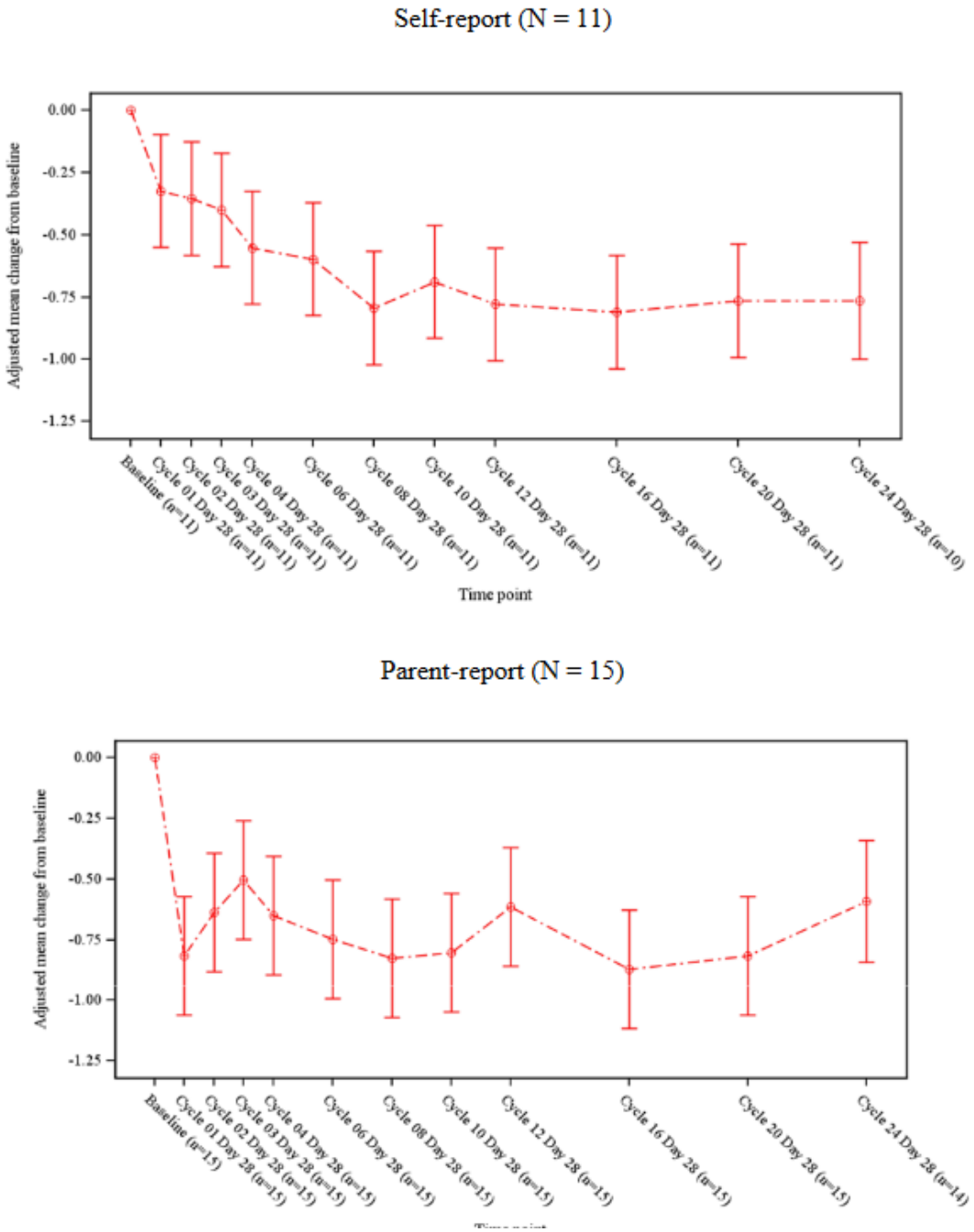
The effect of selumetinib on pain was assessed through (1) self-evaluation of the worst pain intensity (Faces Pain Scale) that the patient had during the past week and (2) how pain interfered with daily functioning (PII), which was rated by the patient and by the parent. In addition, patients recorded the pain medication that was used in the 1 week prior to randomisation in a pain medication survey. During study treatment, pain medication/analgesia was recorded within concomitant medications.

Figure 4 Adjusted Mean Faces Pain Scale Scores of Paediatric Cohort, Change from Baseline Over Time by MMRM Analysis (Safety Analysis Set) (N = 16)



Children aged 4 to 17 years at enrolment completed Faces Pain Scale. A higher score represents more pain, ie, a decrease in score is favourable. Error bars represent 95% CIs for each respective adjusted mean change from baseline. The analysis was performed using a MMRM analysis of change from baseline for all post-baseline visits, with baseline score in the model as a covariate and scheduled visit as an explanatory variable.
Only visits with more than 10 patients are included.
Baseline was defined as the last result obtained prior to the start of study treatment

Figure 5 Adjusted Mean PII Self-Report/Parent-reported Total Scores in the Paediatric Cohort, Change from Baseline Over Time by MMRM Analysis (Safety Analysis Set)

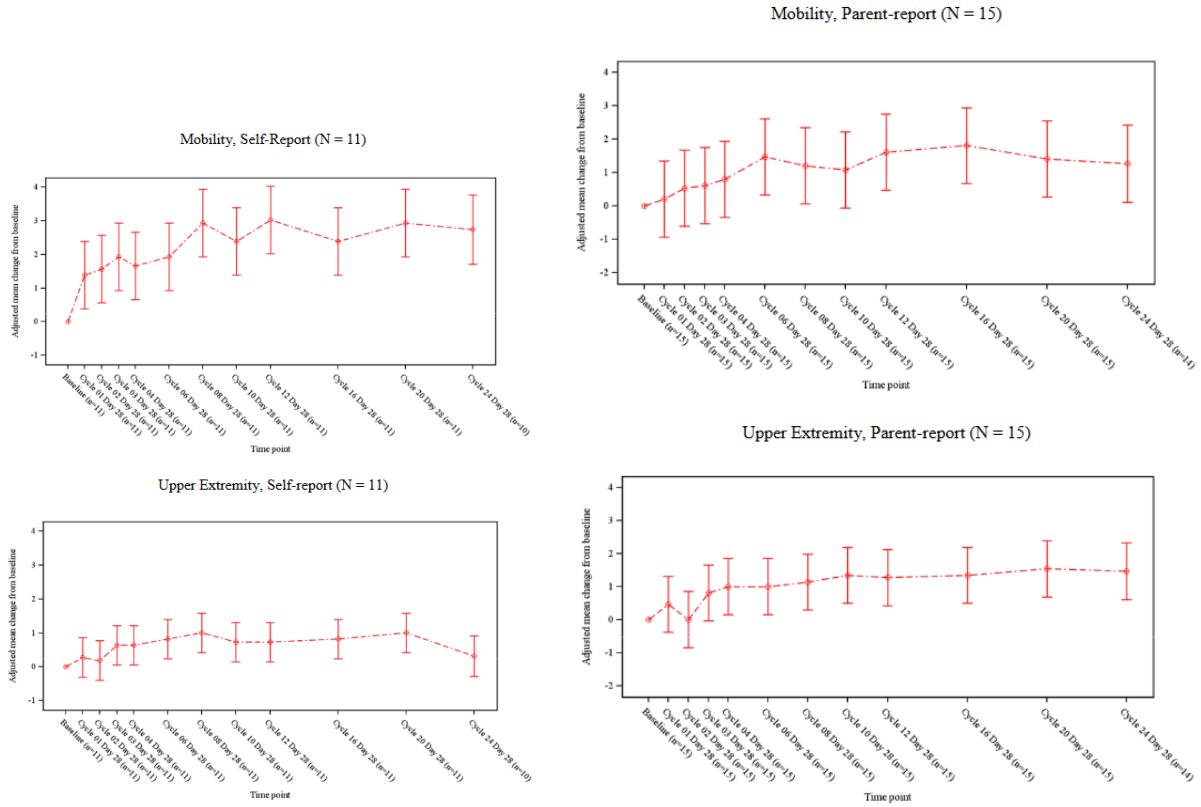


Children from 8 to 17 years of age completed self-reported PII. Parents or the legal guardian of children from 5 to 17 years of age completed the parent proxy PII. A higher score represents more interferences on daily activities. Error bars represent 95% CIs for each respective adjusted mean change from baseline.
The analysis was performed using a MMRM analysis of change from baseline for all post-baseline visits, with baseline score in the model as a covariate and scheduled visit as an explanatory variable.
Only visits with more than 10 patients are included. Baseline was defined as the last result obtained prior to the start of study treatment.

Physical functioning assessment

The PROMIS consists of 8 items using a 5-point Likert scale format (ie, 1 = unable to do, 5 = can do without any difficulty), with a full score of 40.

Figure 6 Adjusted Mean PROMIS Self-/Parent-reported Mobility and Upper Extremity Scores, Change from Baseline Over Time by MMRM Analysis – Paediatric Cohort – Raw Scores (Safety Analysis Set)

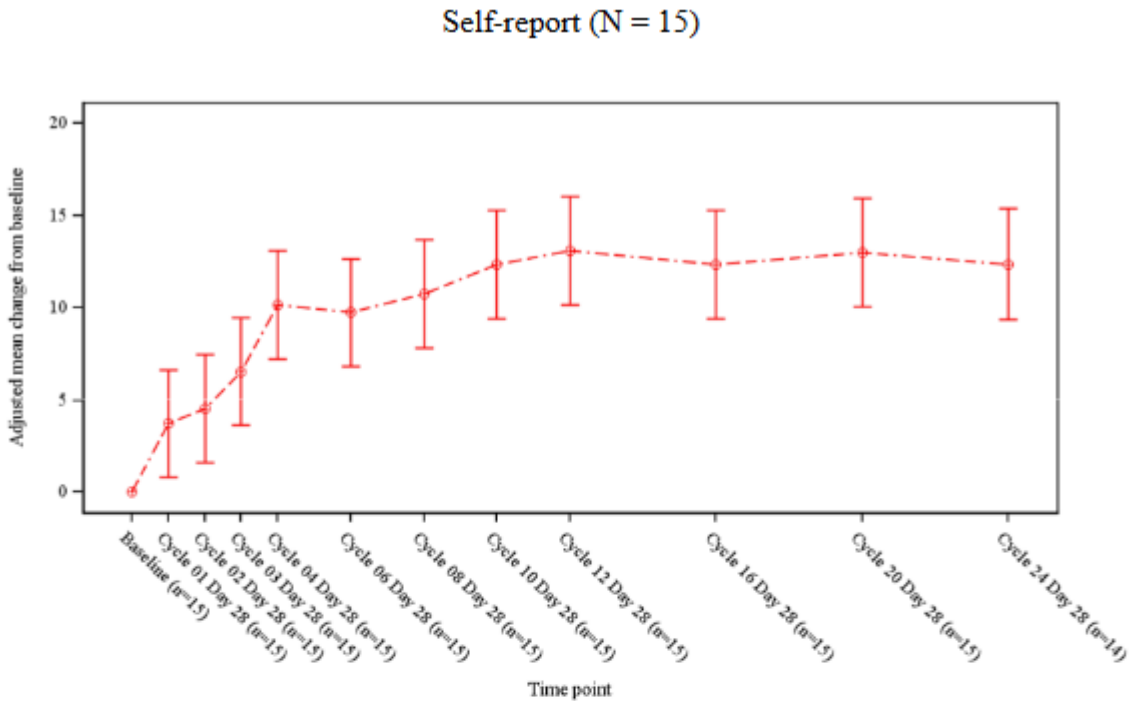


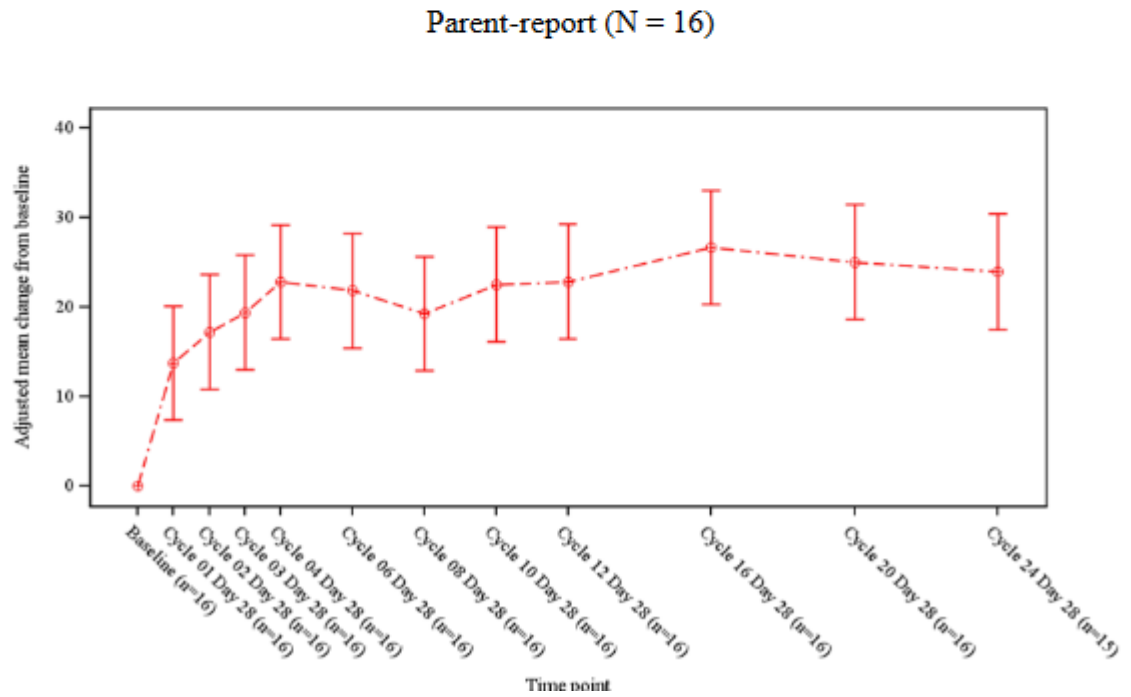
Paediatric cohort completed PROMIS mobility and upper extremity. Parents or the legal guardian completed the parent-reported questionnaire for patients aged 5 to 17 years. A higher score is favourable.
Error bars represent 95% CIs for each respective adjusted mean change from baseline. Baseline was defined as the last result obtained prior to the start of study treatment.
The analysis was performed using a MMRM of change from baseline for all post-baseline visits, with baseline score in the model as a covariate and scheduled visit as an explanatory variable. Only visits with more than 10 patients were include

HRQoL Assessment

PedsQL consists of 4 subscales, ie, physical functioning, emotional functioning, social functioning, and school functioning. For PedsQL, 0 = almost always a problem and 100 = never a problem, where higher scores indicate better HRQoL. A Total Scale Score is the average across all items answered across all the 4 scales

Figure 7 Adjusted Mean PedsQL Self-/Parent-reported Total Score, Change from Baseline Over Time by MMRM Analysis - Paediatric Cohort – Transformed Scores (Safety Analysis Set)





The paediatric cohort completed PedsQL. Patients aged 5 to 17 years completed the self-report questionnaire. The parent-report questionnaire was to be completed for all age groups. A higher score indicates better QoL, so an increase in score is favourable.
Error bars represent 95% CIs for each respective adjusted mean change from baseline.
Baseline was defined as the last result obtained prior to the start of study treatment. The analysis was performed using a MMRM analysis of change from baseline for all post-baseline visits, with baseline score in the model as a covariate and scheduled visit as an explanatory variable. Only visits with more than 10 patients are included.

Adult cohort

Objective Response Rate was provided but not shown here.

Target PN Volume Changes

The analysis of change in target PN volume only included the data from scheduled visits completed within the time window specified in the protocol. In general, all 16 patients had at least one post-baseline assessment and had the chance to complete the Cycle 24 assessment.

TTR and DoR

TTR and DoR analysis were included but not shown here.

Progression-free Survival

As of this DCO, based on investigator assessment, no patient had PD, and the median PFS was not reached. The investigator-assessed PFS rate at 24 cycles was 100%.

Time to Progression

As of this DCO, based on investigator assessment or ICR assessment, the median TTP was not reached.

Pain Assessment

The effect of selumetinib on pain was assessed through (1) self-evaluation of pain intensity (NRS-11) of the target PN selected by the physician, overall tumour pain, and overall pain, and (2) self-evaluation of the extent to which the pain interfered with daily functioning (PII). In addition, patients recorded the pain medication that was used in the one week prior to randomisation in a pain medication survey. During study treatment, pain medication was recorded within concomitant medications.

Physical Functioning Assessment

Physical function in the adult cohort was measured by the PROMIS short form; the overall compliance rate of the assessment was 96.8%.

HRQoL Assessment

The effect of selumetinib on HRQoL was evaluated using the EORTC QLQ-C30 and PlexiQoL for the adult cohort.

Safety results

- Paediatric cohort

At this DCO (15 August 2023), the median (min, maximum [max]) actual treatment duration was 22.80 (18.5, 30.8) months and the median total treatment duration was 23.26 (18.5, 30.8) months.

All 16 patients had at least one AE:

Table 24 Number of Paediatric Patients with AEs in Any Category - Patient Level and Episode Level (Safety Analysis Set)

AE category	Paediatric (N = 16)	
	Number (%) of patients [a]	Number of events
Any AE	16 (100)	161
Any AE possibly related to treatment [b]	16 (100)	73
Any AE of CTCAE Grade 3 or higher	3 (18.8)	6
Any AE of CTCAE Grade 3 or higher, possibly related to treatment [b]	0	0
Any AE with outcome of death	0	0
Any AE with outcome of death, possibly related to treatment [b]	0	0
Any SAE (including events with outcome of death)	3 (18.8)	5
Any SAE (including events with outcome of death), possibly related to treatment [b]	0	0
Any AE leading to discontinuation of IP	0	0
Any AE leading to dose reduction of IP [c]	0	0
Any AE leading to dose interruption of IP [c]	10 (62.5)	11
Any AE leading to dose modification of IP (interruption or reduction)	10 (62.5)	11
Any AESIs	7 (43.8)	15
Any AESIs of CTCAE Grade 3 or higher	0	0
Any other significant AEs [d]	0	0

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] As assessed by the investigator.
[c] If an AE resulted in both transient dose reduction and dose interruption, the measures taken for the AE were recorded as "dose interruption" in the eCRF.
[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 between date of first dose and 30 days following date of last dose. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsened during this period. Patients who had an AE leading to discontinuation of treatment after the DCO date, have been reset to the action taken at the

The most common AEs (> 30%) were COVID-19, pyrexia, upper respiratory tract infection, blood albumin decreased, hyperuricaemia, paronychia, and rash. Except for COVID-19, most were known adverse drug reactions (ADRs) for selumetinib.

Table 25 Number of Paediatric Patients with AEs by SOC and PT (Safety Analysis Set)

SOC / PT	Number (%) of patients [a] (N = 16)
Patients with any AE	16 (100)
Infections and Infestations	**14 (87.5)**
COVID-19	10 (62.5)
Upper respiratory tract infection	7 (43.8)
Paronychia	6 (37.5)
Bronchitis	1 (6.3)
Conjunctivitis	1 (6.3)
Gastroenteritis	1 (6.3)
Influenza	1 (6.3)
Sepsis	1 (6.3)
Skin infection	1 (6.3)
Urinary tract infection	1 (6.3)
Investigations	**12 (75.0)**
Blood albumin decreased	6 (37.5)
ALT increased	4 (25.0)
AST increased	4 (25.0)
Blood CPK increased	4 (25.0)
Haemoglobin decreased	3 (18.8)
Blood urea increased	1 (6.3)
Blood uric acid increased	1 (6.3)
ECG abnormal	1 (6.3)
Intraocular pressure increased	1 (6.3)
Weight increased	1 (6.3)
Skin and Subcutaneous Tissue Disorders	**10 (62.5)**
Rash	5 (31.3)
Dermatitis atopic	3 (18.8)
Eczema	3 (18.8)
Dry skin	2 (12.5)
Blister	1 (6.3)
Dermatitis acneiform	1 (6.3)

SOC / PT	Number (%) of patients [a] (N = 16)
Drug eruption	1 (6.3)
Xeroderma	1 (6.3)
General Disorders and Administration Site Conditions	**9 (56.3)**
Pyrexia	7 (43.8)
Fatigue	1 (6.3)
Influenza like illness	1 (6.3)
Non-cardiac chest pain	1 (6.3)
Injury, Poisoning, and Procedural Complications	**9 (56.3)**
Injury corneal	4 (25.0)
Animal scratch	1 (6.3)
Ankle fracture	1 (6.3)
Arthropod sting	1 (6.3)
Limb injury	1 (6.3)
Multiple injuries	1 (6.3)
Skin injury	1 (6.3)
Gastrointestinal Disorders	**8 (50.0)**
Abdominal pain upper	2 (12.5)
Stomatitis	2 (12.5)
Vomiting	2 (12.5)
Diarrhoea	1 (6.3)
Enteritis	1 (6.3)
Mouth ulceration	1 (6.3)
Metabolism and Nutrition Disorders	**6 (37.5)**
Hyperuricaemia	6 (37.5)
Eye Disorders	5 (31.3)
Ocular hypertension	2 (12.5)
Conjunctivitis allergic	1 (6.3)
Corneal exfoliation	1 (6.3)
Trichiasis	1 (6.3)
Ulcerative keratitis	1 (6.3)
Respiratory, Thoracic, and Mediastinal Disorders	**5 (31.3)**
Cough	2 (12.5)
Rhinorrhoea	2 (12.5)
Nasal obstruction	1 (6.3)
Productive cough	1 (6.3)

SOC / PT	Number (%) of patients [a] (N = 16)
Blood and Lymphatic System Disorders	**2 (12.5)**
Anaemia	2 (12.5)
Musculoskeletal and Connective Tissue Disorders	2 (12.5)
Rhabdomyolysis	1 (6.3)
Scoliosis	1 (6.3)
Nervous System Disorders	1 (6.3)
Headache	1 (6.3)
Cardiac Disorders	1 (6.3)
Ventricular extrasystoles	1 (6.3)
Renal and Urinary Disorders	1 (6.3)
Haematuria	1 (6.3)

[a] Number (%) of patients with any AEs.

Sorted by frequency for SOC and PT.

Patients with multiple AEs were counted once for each PT.

Includes AEs between date of first dose and 30 days following date of last dose. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsened during this period.

MedDRA version 26.0.

Source: Table 14.3.2.3.

All 16 patients reported at least one treatment-related adverse event (TRAE).

Table 27 Number of Paediatric Patients with AEs, Possibly Related to Study Treatment, by SOC and PT (Safety Analysis Set)

SOC / PT	Number (%) of patients [a] (N = 16)
Patients with any AE possibly related to study treatment [b]	16 (100)
Investigations	**10 (62.5)**
Blood albumin decreased	5 (31.3)
Blood CPK increased	4 (25.0)
Haemoglobin decreased	3 (18.8)
ALT increased	2 (12.5)
AST increased	2 (12.5)
Blood urea increased	1 (6.3)
Blood uric acid increased	1 (6.3)
ECG abnormal	1 (6.3)
Intraocular pressure increased	1 (6.3)
Skin and Subcutaneous Tissue Disorders	**8 (50.0)**
Rash	5 (31.3)
Dermatitis atopic	3 (18.8)
Eczema	2 (12.5)
Dermatitis acneiform	1 (6.3)
Drug eruption	1 (6.3)
Dry skin	1 (6.3)
Infections and Infestations	**7 (43.8)**
Paronychia	6 (37.5)
Conjunctivitis	1 (6.3)
General Disorders and Administration Site Conditions	**5 (31.3)**
Pyrexia	3 (18.8)
Fatigue	1 (6.3)
Non-cardiac chest pain	1 (6.3)
Metabolism and Nutrition Disorders	**5 (31.3)**
Hyperuricaemia	5 (31.3)

SOC / PT	Number (%) of patients [a] (N = 16)
Eye Disorders	**3 (18.8)**
Ocular hypertension	2 (12.5)
Corneal exfoliation	1 (6.3)
Blood and Lymphatic System Disorders	**2 (12.5)**
Anaemia	2 (12.5)
Gastrointestinal Disorders	**2 (12.5)**
Mouth ulceration	1 (6.3)
Stomatitis	1 (6.3)
Musculoskeletal and Connective Tissue Disorders	**1 (6.3)**
Rhabdomyolysis	1 (6.3)
Renal and Urinary Disorders	1 (6.3)
Haematuria	1 (6.3)

[a] Number (%) of patients with any AEs possibly related to study treatment.
[b] As assessed by the investigator.

Sorted by frequency for SOC and PT.
Patients with multiple AEs were counted once for each SOC and PT.
Includes AEs between date of first dose and 30 days following date of last dose. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsened during this period.
MedDRA version 26.0.
Source: Table 14.3.2.4.

Most reported AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2. There were 6 AEs of CTCAE Grade 3 that were reported in 3 (18.8%) patients. There were 3 (18.8%) patients with 5 AEs that were classed as serious adverse events (SAEs). All were assessed as not related to treatment. There were no CTCAE Grade 4 or 5 AEs:

- A patient who had D-j ureteral catheterisation and resection of retroperitoneal plexus neurofibroma on 19 December 2017, reported CTCAE Grade 3 sepsis which resulted in a dose interruption after 137 days of selumetinib treatment, and reported another event of CTCAE Grade 3 sepsis together with CTCAE Grade 3 urinary tract infection after 181 days of treatment. None of the 3 SAEs were assessed as treatment related. The investigator considered that the sepsis and urinary tract infection could be related to long-term D-j ureteral catheterisation. All 3 events were resolved.

- A patient had CTCAE Grade 3 scoliosis (verbatim: scoliosis worsened) reported after 303 days of selumetinib treatment, reported as serious after 693 days of treatment. The AE was not assessed as treatment related and the dose was not changed. The AE had not resolved by the time of the DCO.

- A patient had CTCAE Grade 3 multiple injuries (after being hit, kicked, twisted, bitten, or scratched by someone) reported after 385 days of selumetinib treatment. The AE was not assessed as treatment related and the dose was not changed. The event was resolved.

No deaths were reported.

No patients experienced AEs which led to study treatment discontinuation or dose reduction. A total of 10 (62.5%) patients experienced AEs which led to dose interruption.

Table 29 Number of Paediatric Patients with AEs Leading to Dose Interruption of Study Treatment, by SOC and PT (Safety Analysis Set)

SOC / PT	Number (%) of patients [a] (N = 16)
Patients with any AE leading to dose interruption	10 (62.5)
Infections and Infestations	**9 (56.3)**
COVID-19	8 (50.0)
Sepsis	1 (6.3)
Eye Disorders	**1 (6.3)**
Ocular hypertension	1 (6.3)
Skin and Subcutaneous Tissue Disorders	**1 (6.3)**
Rash	1 (6.3)

[a] Number (%) of patients with AEs leading to dose interruption.
Sorted by internationally accepted order for SOC and alphabetical PT.
Patients with multiple AEs were counted once for each SOC and PT.
Includes AEs between date of first dose and 30 days following date of last dose. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsened during this period.
MedDRA version 26.0.
Source: Table 14.3.2.7 (data from AE eCRFs).

Seven patients (43.8%) reported adverse events of special interest (AESIs), most of which were known ADRs of selumetinib and none of which were CTCAE Grade 3 or higher.

Table 30 Number of Paediatric Patients with AESIs, by Grouped Term and PT

Grouped term / PT	Number (%) of patients [a] (N = 16)
Patients with any AESI	7 (43.8)
Hepatotoxicity	**4 (25.0)**
ALT increased	4 (25.0)
AST increased	4 (25.0)
Muscular Toxicity	**5 (31.3)**
Blood CPK increased	4 (25.0)
Rhabdomyolysis	1 (6.3)

[a] Number (%) of patients with AESIs.
Sorted alphabetically for grouped AESI term and PT.
Patients with multiple AEs were counted once for each grouped AESI term and PT.
Includes AEs between date of first dose and 30 days following date of last dose. Includes AEs with an onset date during this period and those with an onset date prior to dosing which worsened during this period.
MedDRA version 26.0.
Source: Table 14.3.2.10.

Case of rhabdomyolysis (not currently listed under the section 4.8 of Koselugo SmPC): A patient had a CTCAE Grade 1 TRAE of corneal exfoliation. The reported text from the investigator was "The subnasal corneal epithelium of the right eye was lightly desquamated". The event started on Day 450 and resolved after 79 days, with treatment given. There was no change to planned study treatment. The same patient had a CTCAE Grade 2 TRAE of rhabdomyolysis. The AE started on Day 450 and resolved after 10 days, with no treatment given. There was no change to planned study treatment. The patient had their Cycle 16 visit on Day 450 and CK was 638 U/L (reference range 26 to 192), approximately 3 times the upper limit of normal. This fell at Cycle 20 (193 U/L) and Cycle 24 (196 U/L). According to data on file, the patient had both lower limbs pain, tenderness, mild lower limbs oedema, symptoms of frequent urination, urgency, no dysuria, and normal urine colour. Routine urine examination revealed haematuria, and routine urine examination returned to normal the next day. The investigator considered that the AE was possible rhabdomyolysis.

No trends of unexpected clinically significant changes were observed in clinical laboratory_evaluation, vital signs, electrocardiogram (ECG)/ echocardiogram (ECHO), and Tanner stages.

No death was reported.

- Adult cohort

At the DCO, the median (min, max) actual treatment duration was 23.69 (7.5, 30.9) months and the median total treatment duration was 25.08 (8.6, 31.3) months.

All 16 patients had at least one AE. The most common AEs (> 40%) were dermatitis acneiform, hyperphosphatemia, AST increased, conjunctivitis, and hyperuricaemia, most of which were known ADRs for selumetinib.

All 16 patients reported at least one TRAE. Most reported AEs were CTCAE Grade 1 or 2. AEs of CTCAE Grade 3 were reported in 4 (25.0%) patients (one event in each patient); 2 were considered possibly related to treatment.

Two (12.5%) patients reported 2 SAEs; both were considered unrelated to treatment. There were no CTCAE Grade 4 or 5 AEs. No deaths were reported. No patients experienced AEs that led to study treatment discontinuation. 7 (43.8%) patients experienced AEs that led to dose interruption. One (6.3%) patient reported an AE of paronychia of CTCAE Grade 3 which was assessed to be treatment related and led to permanent dose reduction. A total of 13 patients (81.3%) reported AESIs, all of which were known ADRs of selumetinib. No trends of unexpected clinically significant changes were observed in clinical laboratory evaluation, vital signs, ECG, and ECHO.

No unexpected significant changes were observed in clinical laboratory evaluation, vital signs, ECG and ECHO.

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 Chinese Paediatric and Adult Patients with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN).

A total of 16 patients aged 4 to 16 years were treated in the paediatric cohort and 16 patients in the adult cohort. Patients received oral doses of selumetinib 25 mg/m2 BID continuously for 28-day until progressive disease (PD) based on the investigator's decision or unacceptable drug-related toxicity, whichever occurred first.

There was no primary efficacy endpoint for this study. The secondary objectives were objective response rate (ORR), target PN volume change, time to response (TTR), duration of response (DoR), time to progression (TTP), and progression-free survival (PFS), based on investigator and independent central review (ICR) assessment per the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. Clinical outcomes included, effect of selumetinib on pain, physical functioning, and quality of life.

Paediatric cohort:

The observed Objective Response Rate (ORR) on the target tumour volume, was 81.3% (95% IC 54.5%, 96%) based on investigator assessment and62.5% (95% IC 35.4.0%, 84.8%) based on ICR assessment. No patients had a complete response. The median TTR was 3.7 (95% CI: 3.55, 7.39) months based on investigator assessment, and 8.7 (95% CI: 3.55, 9.30) months based on ICR assessment.

The median DoR, PFS, and TTP were not reached.

A trend over improvement in pain and physical functional assessment was observed.

Adult cohort:

No patients had a complete response. The median DoR, PFS, and TTP were not reached. A trend over improvement in pain and physical functional assessment was observed.

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 patients included and the open-label design of the study.

Safety outcomes from both cohorts paediatric and adults have been displayed in this AR in order to capture any new signal or trend.

On a safety aspect the provided data are consistent with the safety profile of selumetinib as displayed 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 cohort of 16 paediatric and 16 adult Chinese patients 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 D1346C00011 study, no new safety or efficacy concerns have been identified as compared to previous studies and experiences in patients treated with Koselugo.

☒ **Fulfilled:**

No regulatory action required.