13 November 2025
EMA/392597/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Koselugo

International non-proprietary name: selumetinib

Procedure No. EMEA/H/C/005244/X/0018/G

Note

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

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List of abbreviations

Abbreviation or special term	Explanation
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{0-12}	area under the concentration-time curve from time 0 to 12 hours
AUC_{ss}	area under the concentration-time curve at steady state
bid	2 times a day
BSA	body surface area
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CPK	creatine phosphokinase
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document (Dossier)
D1	duration of the zero-order absorption rate
DCO	data cut-off
DoR	duration of response
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	Europe, the Middle East and Africa
F1	relative bioavailability
fbe	free base equivalent
FD&C	Federal Food, Drug, and Cosmetic
FEV1	forced expiratory volume in 1 second
gCV	geometric coefficient of variation
GDB	glycerol dibehenate
HDPE	High Density Polyethylene
HPMCAS	hypromellose acetate succinate
HPMCAS-LG	hypromellose acetate succinate-LG
HRQoL	health-related quality of life
HV	Healthy volunteer

Abbreviation or special term	Explanation
ICH	International Council for Harmonisation
ICR	independent central review
IND	Investigational New Drug
ISS	integrated safety summary
Ka	first order absorption rate constant
KF	Karl Fischer titration
LDPE	Low density polyethylene
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen activated protein kinase
MSC	Melt-spray-congeal
NCA	noncompartmental analysis
NCI	National Cancer Institute
NDA	New Drug Application
NF1	neurofibromatosis type 1
NMT	Not more than
NS-OEG	Nitrosamines operational expert group
NSAIDS	nonsteroidal anti-inflammatory drugs
ORR	objective response rate
PASS	Post-Authorisation Safety Study
PBPK	physiologically based PK
PBRER	Periodic Benefit Risk Evaluation Report
PDCO	Pediatric Committee
PET	Polyester
Ph. Eur.	European Pharmacopoeia
PIP	Pediatric Investigation Plan
PK	pharmacokinetic(s)
PN	plexiform neurofibroma
POB	Pediatric Oncology Branch
PopPK	population PK
PPSR	Proposed Pediatric Study Request
PSA	parallel scientific advice
PT	Preferred Term
QC	Quality Control
QTPP	Quality target product profile
RAF-MEK-ERK	rapidly accelerated fibrosarcoma-mitogen activated protein kinase-extracellular signal regulated kinase
RAS	renin angiotensin system
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis

Abbreviation or special term	Explanation
RH	Relative humidity
RSE	relative standard error
SA50	stearic acid 50
SAE	serious adverse event
SAP	statistical analysis plan
SMG	stearoyl macrogol-32 glycerides
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SRC	Safety Review Committee
TAMC	Total Aerobic Microbial Count
t_{max}	time to maximum concentration
TYMC	Total Combined Yeasts/Moulds Count
uHPLC	Ultra-high performance liquid chromatography
V2	selumetinib volume of distribution of central compartment
WR	Written Request

1. Background information on the procedure

1.1. Submission of the dossier

AstraZeneca AB submitted on 22 November 2024 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		**Type**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Extension application to introduce a new pharmaceutical form (Granules in capsules for opening) associated with new strengths (5 mg and 7.5 mg capsule) grouped with a Type II variation (C.I.4) to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to align the SmPC and labelling of Koselugo capsules and Koselugo granules in capsules for opening. The Package Leaflet and Labelling are updated accordingly. The RMP version 3.1 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The MAH applied for the following indication for Koselugo 5 mg and 7.5 mg granules in capsules for opening:

Koselugo as monotherapy is indicated for the treatment of paediatric patients aged 1 year to less than 7 years with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Koselugo, was designated as an orphan medicinal product EU/3/18/2050 on 31 July 2018 in the following condition: Treatment of neurofibromatosis type 1.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0134/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0134/2024 was completed.

The PDCO issued an opinion on compliance for the PIP - P/0134/2024, as confirmed by compliance check procedure EMEA/PE/0000223759.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal product Ezmekly (mirdametinib) which has been granted a Marketing Authorisation on 17 July 2025.

1.5. Protocol assistance

The MAH received Scientific Advice on the development of Selumetinib for treatment of neurofibromatosis type 1 and plexiform neurofibromas from the CHMP on 15 October 2020 (EMEA/H/SA/2400/3/2020/PA/PED/III). The Protocol assistance pertained to quality, non-clinical and clinical aspects.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Mari Thorn

The PDCO provided a positive opinion on the agreed paediatric investigation plan.	18 October 2024
The application was received by the EMA on	22 November 2024
The procedure started on	27 December 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 March 2025
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	25 April 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	11 July 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 August 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH	18 September 2025

on	
The MAH submitted the responses to the CHMP List of Outstanding Issues on	09 October 2025
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 October 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Koselugo on	13 November 2025
The CHMP adopted a report on similarity of Koselugo with Ezmekly on (see Appendix on similarity)>	13 November 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

NF1 is a rare autosomal dominant, clinically heterogeneous, genetic disorder characterized by progressive cutaneous, neurological, skeletal, and neoplastic manifestations. NF1 is caused by mutations in the NF1 tumour suppressor gene (17q11.2) which encodes the tumour suppressor protein neurofibromin-1. Neurofibromin-1 is a negative regulator of RAS and therefore loss of function mutations in 17q11.2 lead to a failure to inactivate RAS, resulting in activation of the RAF-MEK-ERK pathway.

2.1.2. Epidemiology

Studies that included both adult and paediatric populations reported prevalence estimates of NF1 between 20 per 100000 and 24 per 100000 persons (Huson et al. 1989; Poyhonen et al. 2000; Evans et al. 2010; Kallionpää et al. 2018), whereas, studies focusing only on paediatric populations or adolescents found slightly higher prevalence estimates ranging from 18 per 100000 to 34 per 100000 persons (Poyhonen et al. 2000; Lammert et al. 2005; McKeever et al. 2008). Approximately half of NF1 cases are familial, with penetrance being 100%, and the remainder are the result of de novo (spontaneous) mutations (Evans et al. 2010).

2.1.3. Aetiology and pathogenesis

Neurofibromin 1 is a guanosine 5' triphosphate (GTP)ase activating protein that promotes the conversion of active RAS GTP to inactive RAS guanosine 5’-diphosphate, thereby functioning as a negative regulator of the RAS proto oncogene, which is a key signalling molecule in the control of cell growth (Gutmann et al. 2012). NF1 mutation that leads to loss of function results in a failure to inactivate RAS. Affected individuals start life with 1 mutated (non-functional) copy and 1 functional copy of NF1 in every cell in their body. Although many of the clinical features of this syndrome are apparent from birth, complete loss of gene function is needed for formation of tumours (including PN), by acquisition of a somatic NF1 mutation in selected cells (Ruggieri et al. 2001; Gutmann et al.

2013b). Patients with NF1 have an increased risk of developing tumours of the central and peripheral nervous system. PNs are one of the most common benign tumours which occur in approximately 20% to 50% of patients (Korf. 1999; Mautner et al. 2008).

Malignant peripheral nerve sheath tumours (MPNST) often arise in pre-existing PNs and whilst MPNSTs are rare in the general population, the lifetime risk of developing MPNSTs in patients with NF1 is estimated to be 8 to 15.8% (Evans et al. 2002; Nguyen et al. 2011; Uusitalo et al. 2015). The incidence of MPNST has been estimated to be 4.6% in patients with NF1 compared to 0.001% in the general population (Ducatman et al. 1986). Other tumours associated with NF1 include low grade gliomas, with optic pathway gliomas occurring in ~15% of NF1 patients, as well as malignant tumours such as high-grade gliomas, breast cancer, leukaemia, pheochromocytomas and gastrointestinal stromal tumours (Gutmann et al. 2017).

NF1 is characterised by progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and the associated clinical signs and symptoms (also referred to as morbidities in the literature and clinical community) can be severe.

Pathophysiology of NF1-related plexiform neurofibromas (PNs)

Neurofibromas are histologically benign nerve sheath tumours, which can be broadly grouped into dermal neurofibromas or PNs. Dermal neurofibromas originate from terminal nerve branches in the skin, rarely developing before puberty, whereas PNs typically grow along large nerves and plexuses and are present at birth (Hannema and Oostenbrink. 2017). PN manifestations vary and may continue to become apparent through late adolescence and early adulthood (Williams et al. 2009). Typical PNs are clinically distinct from localised (or 'nodular' or 'atypical') neurofibromas in that they have potential for malignant transformation and are considered by some to be pre-malignant (Gutmann et al. 2017; Higham et al. 2018).

PNs can have complex shapes and sometimes reach very large size, with some documented as being 20% of body weight (Korf. 1999; Mautner et al. 2008). PNs may develop along nerves anywhere in the body, and may be located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, and neurological dysfunction.

2.1.4. Clinical presentation, diagnosis

Diagnosis of NF1

Due to the rarity of the disease, the diagnostic criteria for NF1 were defined at a National Institute of Health (NIH) consensus development conference in 1987 (National Institutes of Health Consensus Development Conference, 1987).

In most cases, the diagnosis of NF1 is made on clinical grounds, requiring 2 or more clinical features to be present from the defined list of diagnostic criteria for NF1 presented below:

- Six or more café-au-lait macules (diameters ≥0.5 cm in pre-pubertal patients or ≥1.5 cm in post-pubertal patients)
- Two or more neurofibromas or 1 PN
- Freckling in axilla or groin
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)

- A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)

- First-degree relative with NF1 (diagnosed using the above criteria).

Genetic testing is performed in rare circumstances and not advocated routinely.

Neurofibromas are histologically benign nerve sheath tumours, which can be broadly grouped into dermal neurofibroma or PN. Dermal neurofibromas originate from terminal nerve branches in the skin, rarely developing before puberty, whereas PNs typically grow along large nerves and plexuses and are present at birth.

Growth of PNs

It has been observed that older patients have slower growing PNs when compared to younger patients (Dombi et al. 2007; Nguyen et al. 2012; Gross et al. 2018; Akshintala et al. 2020). PNs grow most rapidly during the first decade of life and whilst growth rate is highly variable between patients, the growth rate of PNs in younger children is generally much greater compared with that in older children or adults (Dombi et al. 2007; Tucker et al. 2009; Nguyen et al. 2012). It has been demonstrated that the PN growth rate in children exceeded the rate of increase in their body weight (Dombi et al. 2007) or body mass index (Tucker et al. 2009), so the rapid tumour growth cannot be attributed to the anticipated growth rate of a child.

It has also been observed that larger PNs are associated with slower growth (Akshintala et al. 2020).

In the scientific literature the following median PN growth rates can be found: +14.3%/year (Dombi et al. 2007); +2.8%/year (Nguyen et al. 2012); +15.9%/year (Gross et al. 2018); +12.4%/year (Akshintala et al. 2020).

Spontaneous shrinkage of PNs has been described, but never exceeding -20%/year (Dombi et al. 2007; Nguyen et al. 2012; Akshintala et al. 2020). For example, Nguyen et al. reported that 35.5% of tumours had smaller volumes on follow up, with a median measured change in volume of −3.4%/year (Nguyen et al. 2012). Akshintala et al. applied a stricter definition for spontaneous tumour volume reduction to exclude e.g. measurement error. They reported that although in 47/113 PNs (41.6%) the final volume was less than the maximal volume during the entire period of follow-up, only in 10/113 PNs (8.8%), spontaneous shrinkage could be confirmed, with a median decrease from maximum volume of 19.0% and a median decrease per year of 3.6% (Akshintala et al. 2020). Of note, all these publications are from the National Cancer Institute (NCI) Paediatric Oncology Branch (POB).

PN associated clinical symptoms

Patients may have 1 or multiple PNs which result in clinical impact such as pain, neurological and motor dysfunction, airway compromise, visual impairment, or disfigurement. The severity may range from mild, with modest impact on daily activities to severe. The symptoms or impact from the presence and growth of PNs are collectively termed PN associated symptoms (also referred to as morbidities in the literature and clinical community) and spontaneous resolution of these symptoms once developed has been shown to be extremely unlikely (Gross et al. 2018).

The presence of PN can cause weakness and restricted range of motion (Gross et al. 2018), and pain associated with PN can also interfere with daily activities despite analgesia (Wolters et al. 2015). PN can result in life-threatening complications due to compression of vital structures (e.g. great vessel compression, spinal cord compression, and airway obstruction). A retrospective data analysis of the clinical records of children with NF1 reported an increased mortality rate has been reported in children with symptomatic PN (5/154 patients, 3.2%) compared to those without PN or with unrecognised/asymptomatic PN (2/366 patients, 0.5%, p=0.024, Prada et al. 2012). The most

common cause of death in patients with NF1-PN was MPNSTs (in 3 patients aged 14 to 21 years), other causes included hypovolemic shock in an 18 year old patient, due to a PN-related haemothorax and respiratory failure in a 3 year-old patient due to airway compression (Prada et al. 2012).

The most common clinical complications leading to surgery were found to be neurologic, disfigurement, orthopaedic, and airway complaints (Prada et al. 2012).

2.1.5. Management

At the time of the initial submission of this application, selumetinib was the only approved product approved for the treatment of symptomatic, inoperable PN in paediatric patients from 3 years of age with NF1.

There is currently one systemic treatment option approved for patients with NF1 PN: Ezmekly (mirdametinib - EMEA/H/C/006460), an oral selective MEK inhibitor, conditionally authorised in the EU in July 2025 for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

2.2. About the product

Selumetinib Hyd-sulfate (hereafter referred to as selumetinib) is a selective, oral, inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) that is not competitive with respect to ATP. MEK1/2 are critical components of the RAS-regulated, RAF-MEK-ERK pathway which is frequently activated in human cancer.

The new proposed formulation, granules in capsules for opening (herein referred to as granule formulation), is proposed for the treatment of paediatric patients from 1 to less than 7 years of age with NF1 who have symptomatic, inoperable PN and also represents an alternative option to the approved capsules in the treatment of paediatric patients 3 years of age to less than 7 years of age with NF1 who have symptomatic, inoperable PN.

2.3. Type of Application and aspects on development

The MAH developed an age-appropriate selumetinib granule formulation which is intended for patients aged from 1 to less than 7 years of age who may have difficulty swallowing capsules.

In consideration for expanding the use of selumetinib (Koselugo), the MAH proposed the addition of this new age-appropriate formulation in line with the latest PIP decision (P/0341/2021).

The MAH received Scientific Advice on the development of Selumetinib for treatment of plexiform neurofibromas in patients with neurofibromatosis type 1 from the CHMP on 15 October 2020 (EMEA/H/SA/2400/3/2020/PA/PED/III).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as granules in capsule for opening containing 5 mg or 7.5 mg of selumetinib (as hydrogen sulfate).

Other ingredients are:

Granule content: glycerol dibehenate, stearoyl macrogol glycerides, hypromellose acetate succinate, stearic acid.

Capsule shell: hypromellose (E464), titanium dioxide (E171), yellow iron oxide (E172) (5 mg capsules), red iron oxide (E172) (7.5 mg capsules)

Printing ink: shellac (E904), propylene glycol (E1520), ammonia solution, concentrated (E527), iron oxide black (E172), potassium hydroxide (E525)

The product is available in high-density polyethylene (HDPE) plastic bottle with child-resistant polypropylene screw closure as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance used to manufacture the 5 and 7.5 mg granules in capsule for opening is the same as that used for the already authorised 10 mg and 25 mg hard capsules. No new information on the active was submitted as part of this line extension application, except the updates described below.

2.4.2.1. Manufacture, characterisation and process controls

An acceptable QP declaration has been provided in annex 5.22 of the module 1 for the active substance manufacturers declared in section S.2.1, based on audits carried our less than 3 years ago.

Modifications declared to section S.2.2 consist in a clarification that unmicronised seed to be used during active substance manufacture would conform to the corresponding specification for intermediate selumetinib hyd-sulfate. No impact on the quality of the active substance is expected.

No changes have been declared to section S.3.

2.4.2.2. Specification

An updated '3.2.S.4.4 Batch Analyses for Drug Substance' is provided, which includes the latest batch analysis data for selumetinib hyd-sulfate used in the manufacture of the new formulation (granules in capsule for opening). In all cases, compliance with the specification approved were shown.

A correction has been made to the sulfated ash specification for the selumetinib free base reference standard in '3.2.S.5 Reference Standards or Materials', to align with the specification limit for sulfated ash stated in '3.2.S.4.1 Specification for Drug Substance' (change from NMT 0.1% to NMT 0.2%).

No changes have been declared to sections 3.2.S.6.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product consists of selumetinib hyd-sulfate granules in capsule for opening packed into a HDPE bottle with polypropylene child-resistant screw cap. The finished product is presented under two strengths filled with a common coated granule:

– 5 mg (selumetinib free base equivalent) in Size 0 capsule with a yellow cap and a white body printed with 'sel 5' and a sprinkle capsule image indicating opening, and

– 7.5 mg (selumetinib free base equivalent) in Size 0 capsule with a pink cap and a white body printed with 'sel 7.5' and with a sprinkle capsule image indicating opening.

The capsules are to be opened, and the coated granules added to a soft-food vehicle prior to ingestion as described in section 4.2 of the SmPC. The capsule shell is not intended to be swallowed.

The finished product quantitative and qualitative composition has been provided**1234**.

1 2 3

4 The aim of the formulation development was to produce an appropriate oral dosage form for administration to children with a body surface area of less than 0.55 m^2 (children aged 1 to less than 7 years) or very young children who may have difficulty swallowing capsules, while maintaining the hyd-sulfate and associated bioavailability found for the authorised Koselugo capsules and allowing more flexibility in dosages and improving palatability and swallowability. **55** .

Based on experience from the development of Koselugo capsule formulation, a lipidic formulation was selected. The finished product comprises the active substance (selumetinib hyd-sulfate) dispersed in a lipidic matrix of glycerol dibehenate and stearoyl macrogolglycerides to form uncoated cores, which are subsequently coated with hypromellose acetate succinate (HPMCAS)-LG and stearic acid 50 to prevent dissolution within the soft food dosing vehicle prior to administration and to provide taste masking to improve palatability. Both strengths contain the same coated granules, with the fill weight varied to achieve the required strength. The functionality related characteristics of excipients that may have an impact on the finished product manufacturability were studied. Critical material attributes of excipients have been properly addressed to justify the proposed grades.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, except yellow iron oxide, red iron oxide and black iron oxide which comply with European standards for colouring agents approved for use in pharmaceutical products, and butyl alcohol which complies with FP/USP. This is acceptable since they have a specific Ph. Eur. monograph. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of the active substance with the excipients used in the proposed commercial formulation is confirmed by the results of stability studies on it, which show no chemical or physical degradation (see stability section).

Regarding the comparison between granules and Koselugo capsules, data from the relative bioavailability Study 89 and the SPRINKEL study support the conclusion that the granule formulation could be considered comparable with the capsule formulation in terms of AUC (see pharmacokinetics section).

In the SPRINKLE study, a questionnaire to parents was carried out to evaluate the palatability of the formulation. This study has rather evaluated the compliance and the acceptability of the dosage form than the palatability. Based on the results, the proposed dosage form may be considered as adapted for the patient age (see clinical section).

The formulation used during clinical studies is the same as that intended for marketing, except that the capsule shells used for the clinical and commercial formulations in appearance, and therefore colourant, ink composition and printing. The decision to change the capsule shell colour and ink between the clinical and commercial presentations was based on appearance only. As the capsule shells are not to be ingested, the clinical and the commercial formulation can be considered equivalent.

No overages are included in the formulation of the finished product.

Following a request from CHMP, the applicant has proposed two different dissolution methods for the commercial quality control (QC) release: the first one allows to assess the coat integrity of sprinkled granules in food in order to preserve the taste masking of the active substance, and a second one to evaluate the active substance release. This approach is endorsed.

The first dissolution method is capable of demonstrating full release of selumetinib hyd-sulfate from the selumetinib granules at intestinal pH conditions upon dissolution of the coating. The discriminating effect of the coat integrity test was assessed by testing coat weight %, granule size, process and manufacturing stretch Only coat weight % showed a discriminatory effect of the proposed coat integrity dissolution method.

The second dissolution method was designed to confirm the fast and complete release of the active substance in intestinal conditions, following the fast dissolution of the coat. The discriminating effect of the dissolution method used to evaluate drug release was assessed by testing granule size, process and manufacturing stretch and selumetinib free base-spiked variants. Based on those experiments, manufacturing variability, storage of granules in HDPE bottle and free base content have shown a certain discriminating effect of the proposed dissolution method.

The discriminatory power of both dissolution methods has been demonstrated.

Sufficient information concerning the container closure system have been provided. The primary packaging is High-density polyethylene (HDPE) plastic bottle with child-resistant polypropylene screw closure. The material complies with Ph. Eur. and EC requirements. Inside the cap there is a liner and seal. The liner is made of wax coated pulp board and the seal is an aluminium foil lined with polyethylene. The polyethylene layer is product-facing for the unopened bottle. The seal is induction-sealed to the bottle for tamper evidence. The aluminium foil seal is removed from the bottle when opening the bottle, the first time. There is a desiccant containing silica gel inside the bottle. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The bulk selumetinib granules in capsule for opening are packed in an aluminium foil bag which is sealed. As indicated above and in SmPC section 4.2, Koselugo granules must be administered by carefully opening the capsules and sprinkling the entire contents on a small amount (approximately 1 to 3 teaspoons) of soft food (e.g. smooth yogurt, fruit sauce, fruit puree or fruit jam). The granules must not be mixed in water, milk, vegetable puree, grapefruit or any juice, fruit puree or jam containing Seville orange (bitter orange).

This medicinal product dispensed on or mixed with food must be swallowed within 30 minutes and must not be stored for future use. The empty capsule shells of Koselugo must be discarded after use This restriction of food is based on the fact that the selumetinib granule coat composition was selected to provide a barrier coat which would limit dissolution in the low pH of typical soft food vehicles (such as yogurt, fruit puree or sauce) prior to administration, whilst enabling rapid dissolution in the neutral pH of the small intestine after administration. Water and vegetable puree typically have higher or neutral pH >6 which would compromise the coat integrity, and therefore these are not recommended as dosing vehicles for selumetinib granules. This would not have any relevant effect on the *in vivo* performance when the dose has been ingested but may lead to dissolution of the drug in the vehicle prior to administration and potentially negatively impact the taste for the patient.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at two manufacturing sites: Valid GMP documentation demonstrating GMP compliance has been provided.

The manufacturing process of the finished product is divided into three parts, based two intermediates (uncoated cores, coated granules) and the final product (selumetinib hydsulfate granules in capsule for opening. These include:

- Manufacture of uncoated cores, comprising three-unit operations: blending of the active substance and glycerol dibehenate, a melt-spray-congeal (MSC) process, and screening
- Manufacture of coated granules, comprising two-unit operations: fluid bed coating and drying.
- Selumetinib granules in capsule for opening, comprising one unit operation encapsulation of the granules into HPMC hard capsules. 1

2 Both strengths of finished product are manufactured from a quantitatively identical common coated granule. The capsule fill weight defines the capsule strength. The criticality of the manufacturing process has been discussed and adequately described. A relationship between process stages and the drug product CQAs (description, assay, uniformity of dosage units, dissolution/coat integrity, residual solvent) was identified. In addition, equipment, holding times have been properly presented.

Critical controls of the intermediates – uncoated cores and coated granules have been presented as well as specifications, description and validation of the analytical methods, batch results data, container closure system and stability as well as transportation conditions/monitoring arrangements between the two manufacturing sites for the bulk of coated granules.

For this type of dosage form, the manufacturing process can be considered as a non-standard process (notably the melting/spraying/congealing extrusion step). Therefore, as requested by CHMP during the review (MO), formal validation results via a traditional approach for three commercial scale batches for each strength were provided as well as an ongoing process verification approach to keep the process in a state of control during commercial manufacture. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (UHPLC-UV), assay (UHPLC), degradation products (UHPLC), dissolution (Ph. Eur.), coat integrity (Ph. Eur.), uniformity of dosage units (Ph. Eur., UHPLC), water content (KF) and microbiological quality (TAMC, TYMC, absence of specified microorganisms) (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three commercially representative batches of finished product using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Following a Major Objection (MO) from CHMP, a risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine

impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). This assessment identified a potential risk of the presence of N-nitroso selumetinib, formed by reaction of the active substance itself and nitrites present in the finished product. A toxicology assessment considered the structural similarity of N-nitroso selumetinib to N-nitroso diphenylamine, and the corresponding TD50 animal carcinogenicity data. N-nitroso diphenylamine has an established limit in the EMA N-nitrosamine database of 78000 ng/day. In accordance with 'EMA/409815/2020 Q.10', and based on this read-across assessment (which has been deemed acceptable by the NS-OEG), the acceptable intake for lifetime exposure of N-nitroso selumetinib is 78,000 ng/day. The risk assessment concluded that the theoretical maximum daily exposure of N-nitroso selumetinib is less than 10% of the acceptable intake and is therefore deemed no risk. The risk assessment evaluated all other risk factors and concluded that there was no risk of presence of N-nitrosamines, and therefore a specification clause for N-nitrosamines is not required. Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standard used for the testing of the finished product is the same as that used for the testing of the active substance. Reference is made to section 3.2.S.5. This is acceptable.

Batch analysis results are provided 12 clinical / stability batches for the 5 mg strength and for 18 clinical / stability batches for the 7.5 mg strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Concerning the organic impurities, no significant additional degradation products observed within the finished product compared to the active substance. Also, for mutagenic impurities, an evaluation of the excipients and finished product manufacturing process indicates no risks associated with the finished product in addition to those arising from the active substance. Concerning residual solvents: an ICH Q3C class 3 solvent is used in the coating solution. Its content in 25 clinical batches of finished product was well below the ICH Q3C threshold (0.5%).

2.4.3.4. Stability of the product

Stability data from three pilot scale batches of finished product of each strength stored for up to 24 months under long term conditions (25 ºC / 60% RH and 30°C/75% RH) according to the ICH guidelines were provided. Accelerated stability is not feasible for these formulations due to the melting point of the coated granules which results in physical changes (agglomeration and loss of flowability). This makes testing at such conditions non-representative of actual storage. The data from a short-term investigative study on a clinical batch of 7.5 mg granules in capsules when stored at 40°C/75% RH for 24 hours confirm this behaviour.

Open dish conditions were assessed for one batch of each strength.

In addition, one batch of each product strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

The batches of the finished product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, dissolution, coat integrity, water content and microbiological quality (water activity, TAMC, TYC, absence of *E. coli*). The analytical

procedures for assay and degradation products used during the primary ICH stability studies originally used HPLC and have subsequently been optimised to use UHPLC. Comparative data using both methodologies were generated on samples at the 6-month time point of the primary ICH stability studies. These data demonstrate that these methods are suitably comparable. The new (UHPLC) procedure has been used from the 9-month time point and the old (HPLC) method discontinued. The analytical procedures used are stability indicating.

The primary stability data generated showed little or no change in description, assay, coat integrity, selumetinib acid content or microbiological quality. Some variability is observed between timepoints for the assay results, but there is no trend in the assay results. An increase was observed in the level of an unspecified degradation product for both strengths at 25°C/60%RH and 30°C/75%RH, from as early as the 3-month time point. These increases in degradation products are deemed not significant. There is a small increase in water content which is deemed not significant. For all batches compliance with the specification at 25°C was shown.

In addition, simulated bulk pack stability was assessed for one batch of each strength of selumetinib granules in capsule for opening stored for 24 months at 5°C and under long term conditions (25°C/60% RH and 30°C/75% RH). The batches showed little or no change in description, assay, coat integrity, selumetinib acid content or microbiological quality. Some variability was observed between timepoints for the assay results, but there was no trend in the assay results. An increase was observed in the level of an unspecified degradation product for both strengths at 25°C/60% RH and 30°C/75% RH, from as early as the 3-month time point. As for the primary stability data, there is a corresponding increase in total degradation products based on these increases. These increases in degradation products are deemed not significant. There is a small increase in water content, which is deemed not significant.

Dissolution meets acceptance criteria throughout the study at 25°C/60% RH in both HDPE bottle and aluminium bag. However, multiple failures to meet the same acceptance criteria have been observed for both product strengths in the HDPE bottle and the aluminium bag at 24 months at 30°C/75% RH. Failures at this timepoint and condition have also been observed within the coated granule intermediate. Therefore, shelf-life extrapolation cannot be applied to the selumetinib granules in capsules for opening. Shelf-life will be based on real-time long-term stability data.

In the open-dish conditions there is a significant increase in water content at both 25°C/60% RH and 30°C/75% RH, and a minor increase in selumetinib acid (formed from hydrolysis of selumetinib hyd-sulfate) and largest individual impurity. This results in increased levels of total degradation products. All other data remain in line with the initial data. Some variability is observed in the assay results from timepoint to timepoint. Some individual results are outside specification but there is no trend in the assay results.

When stored under light-exposed conditions there is a significant increase in the largest individual degradation products and water content when compared to the light-protected conditions in the HDPE bottle. All other tests are consistent compared to initial across both conditions. These data show that the capsules should be protected from light, and this is sufficiently provided by the HDPE bottle. The water content increase is due to the open nature of the condition as shown in the open-dish conditions.

In addition, one supporting stability study pilot scale batch each of 5 and 7.5 mg selumetinib granules in capsule for opening manufactured at one of the proposed finished product manufacturing sites have been set down in a stability study. The batches have been stored also at two long-term conditions (25°C/60% RH and 30°C/75% RH) in the commercial bottle configuration stored for up to 48 months. The applicant declares that these clinical batches were manufactured using the same active substance and the same quantitative formulation as the primary stability batches, but with some differences in process and equipment. Batch data presented demonstrate that batches manufactured in this manner

are comparable in quality to batches used in the primary stability study. The stability results from these batches were also in line with the results observed on the primary batches.

Based on available stability data, the proposed shelf-life of 24 months and storage condition to 'not store above 25 ºC' for Koselugo 5 mg and 7.5 mg granules in capsule for opening as stated in the SmPC (section 6.3) are acceptable. The open-dish stability data provide assurance that the in-use stability of the product is 10 weeks when stored at 25°C. A holding time of 12 months has been assigned to selumetinib granules in capsule for opening 5 mg and 7.5 mg, when stored in aluminium bags not above 25°C.

In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

2.4.3.5. Adventitious agents

It is declared that no excipients used in the manufacture of selumetinib granules in capsule for opening are derived from human or animal sources. The printing ink component "shellac" which is derived from an insect.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension application has been submitted to introduce a new pharmaceutical form and strength for Koselugo: 5 and 7.5 mg granules in capsule for opening to enable the administration of selumetinib to children with a body surface area of less than 0.55 m^2 (children aged 1- < 7 years) or very young children who may have difficulty swallowing the authorised Koselugo capsules. Information on development, manufacture and control of the finished product has been adequately addressed as well as the two quality MOs raised during the review regarding the comprehensive risk assessment on nitrosamines impurities (MO1) and the missing process validation data (MO2). The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

2.5. Non-clinical aspects

2.5.1. Introduction

Koselugo is currently approved in children from 3-year-old. The MAH is asking an extension of Marketing Authorisation Application -addition of a new pharmaceutical form (granules in capsules for opening) for paediatric patients aged ≥1 to <7 years old and for older patients with swallowing difficulties; grouped with a Type II variation to align the Product Information of Koselugo hard capsule.

Compared to the currently available hard capsules from 3-year-old, no non-clinical changes were proposed (in SmPC section 5.3, 4.6 and 5.1). For the line extension, a new population is proposed (from 1-year old instead of 3) and a new formulation is proposed in a combined PI: Koselugo 5/7.5 mg granules in capsules for opening. The SmPC section 5.3 is based on multiple animal/human exposures at the MRHD (Maximum Human Recommended Dose) which is 25 mg/m^2 twice daily.

The MAH has submitted a justification of not performing any additional animal study and not submitting module 2.4: excipients usually used in paediatric population and already discussed in the PIP, no need for juvenile animal study requested in the PIP (confirmed in the initial MAA and still valid), which is considered acceptable.

2.5.2. Pharmacokinetics

The MAH didn't provide new non-clinical pharmacokinetics studies

2.5.3. Toxicology

The MAH didn't provide new non-clinical toxicology studies

2.5.4. Ecotoxicity/environmental risk assessment

The MAH has submitted a new Environmental Risk Assessment (ERA) (29/09/2024in line with the new ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr., 2024). However, no new study was performed, compared to the previous ERA version (24/11/2020), the MAH has performed a Phase I and Phase II A and B studies.

To be noticed, according to the revised guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr., 2024) the $PNEC_{groundwater}$ is based on the $PNEC_{surface\ water}$ and an additional AF of 10.

Table 6. Summary of main study results

Substance (INN/Invented Name):	**Selumetinib/KOSELUGO**		
CAS-number (if available):	606143-52-6 (943332-08-9: selumetinib hydrogen sulphate)		
PBT/vPvB screening			
Study type	Test protocol	Result	Conclusion
Bioaccumulation potential- log Kow	OECD 107	1.55	Potential PBT: N
PBT/vPvB assessment			
Property	Parameter	Result	Conclusion

Bioaccumulation	log D_{ow} Selumetinib ionisable molecule (OCDE 107)	Log D_{OW} = 2.55 pH 5 Log D_{OW} = 2.58 pH 7 Log D_{OW} = 1.78 pH 9	Potentially not B
Persistence	DT50 or ready biodegradability (OECD 308)	DT_{50} at 12°C =182 d (transformation product)	Potentially vPP
Toxicity	NOEC (OECD 211)	NOEC daphnia = 0.34 mg/L	not T
PBT/vPvB statement:	The compound is not considered as not PBT		

Phase I

Parameter	Value	Unit	Conclusion
PEC_{sw}	Default PECsw = 0.50 Refined PECsw = 0.017	µg/L	≥ 0.01 threshold: Y

Phase II Physical-chemical properties and fate

Study type	Test protocol	Result	Remarks
Adsorption-Desorption	OECD 106	K_{oc} = 2058 L/Kg < 10000 L/Kg (2 soils, 2 sediments, 1 sludge)	
Biodegradation in sewage sludge	OECD 314B	2% mineralised over the 28-day study period Selumetinib rapidly converted into 3 major (>10%) degradation products Kbiodeg = 0.45 d^{-1}	Primary degradation
Hydrolysis	OECD 111	<10% (120 hours) at pH 5, 7 and 9	Hydrolytically stable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 3.7 - 4.1 d (20°C) $DT_{50, sediment}$ = 1.5 – 30.4 d (20°C) $DT_{50, whole\ system}$ = 4.5 – 30.6 d (20°C) transformation product $DT_{50, water}$ = 17.8 – 22 days (20°C) $DT_{50, whole\ system}$ = 76 days - plateau (20°C) % shifting to sediment = Transformation product (unknown WS1) up to 73.5% > 10% at d100	Transformation of [^{14}C] selumetinib resulted in formation of a stable (very persistent), unidentified TP and incorporation of radioactivity into sediment organic matter
Transformation products		>10% = *Y* selumetinib amide (max) = 73.5 % on day 100 $DT_{50\ totalsystem\ 12°C}$ selumetinib amide: *182* d	

Phase II Aquatic effect studies					
Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	4900	µg/L	
Daphnia sp. Reproduction Test/	OECD 211	NOEC	340	µg/L	
Fish, *Pimephales promelas*	OECD 210	NOEC	4100	µg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{10}	257000	µg/L	total respiration
Phase II Sediment effect studies					
Sediment Dwelling Organism Test/*Chironomus riparius*	OECD 218	NOEC	133	mg/kg_{dw}	not normalised to 10% o.c.; 2.1% o.c.

Risk characterisation				
Compartment	PEC	PNEC	RQ	Conclusion
STP	0.15 µg/L	34 µg/L	<1	No risk
Surface water	0.015 µg/L	34 µg/L	<1	No risk
Groundwater	0.0038 µg/L	3.4 µg/L	<1	No risk
Sediment	1.1 mg/kg_{dw}	1.33 mg/kgdw	<1	No risk

[#]Long chemical names and/or structural formulas are to be inserted below the table for reasons of space.

No environmental risk has been identified, as a consequence of the use of selumetinib sulfate. The labelling proposed by the MAH to reduce any risks to the environment with regards to the administration to patients and disposal of waste products is endorsed:

"Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment." (section 5 of the package leaflet for both formulation).

2.5.5. Discussion on non-clinical aspects

No non-clinical study was included in this application which is acceptable. The new ERA was submitted since a new guideline was adopted but no new study performed, this is acceptable. No risk to the environment is identified.

2.5.6. Conclusion on the non-clinical aspects

From a non-clinical perspective, this extension of MAA is approvable.

2.6. Clinical aspects

2.6.1. Introduction

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Type of study	Study identifier and study design	Objective(s) of the study	No. of participants randomized/ treated
PK and safety studies			
Dose finding (MTD; PK) and safety	D1532C00057 (SPRINT Phase I) Phase I, open-label, single-arm, multiple-dose, dose-escalation, multicenter study of selumetinib in pediatric participants with NF1 and inoperable PN, and was conducted by the NCI POB	**Primary:** To determine the MTD, extended tolerability, and RP2D of selumetinib administered orally every 12 hours on a continuous daily schedule for cycles of 28 days with no rest period between cycles in children and adolescents with NF1 and inoperable PN. The MTD will be defined based on toxicities observed during the first 3 treatment cycles. To study the plasma PK of selumetinib at baseline and steady state. **Secondary:** To determine the effect of selumetinib on the growth of PN; the rate of PN using automated volumetric MRI analysis; to measure adherence of selumetinib chronic dosing in this participant population; and to describe and define the toxicities in pediatric participants on chronic dosing of selumetinib.	24/24
PK and safety	D1346C00015 (GI tolerability) Phase I, single-arm, multiple-dose, uncontrolled, sequential, 2 or 3-period study in adolescent children aged ≥ 12 to < 18 years at study entry with a clinical diagnosis of NF1-related PN	**Primary:** To investigate the effect of a low-fat meal on the PK of selumetinib capsules after multiple doses at 25 mg/m^2; the effect of a low-fat meal on the PK of selumetinib capsules after multiple doses at the adjusted dose (T3); and the GI toxicity of selumetinib capsules after multiple doses under fed conditions (T1 and T3) compared to fasted conditions (T2). **Secondary:** To further assess the safety and tolerability of selumetinib capsules by assessment of all AEs, laboratory variables, and vital signs and to further evaluate the PK of selumetinib and N-desmethyl selumetinib metabolite after multiple doses under fed conditions, compared to fasted conditions.	25/24
PK, safety, and tolerability	D1346C00011 (China PK study in adult and pediatric participants) Open-label, single-arm Phase I study with 2 independent cohorts to assess the safety,	**Primary:** To assess the safety and tolerability of selumetinib in Chinese paediatric and adult participants with NF1 and inoperable PN and to characterize the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Chinese	32/32 (16 adult and 16 pediatric participants) - based on a clinical data cutoff date of 15 August 2023.

Type of study	Study identifier and study design	Objective(s) of the study	No. of participants randomized/ treated
PK and safety studies			
	tolerability, PK, and clinical efficacy of selumetinib.	paediatric and adult participants with NF1 and inoperable PN. **Secondary:** To evaluate the clinical efficacy of selumetinib in Chinese paediatric and adult participants with NF1 and inoperable PN on ORR, DoR, PFS, TTP, and TTR; to evaluate the effect of selumetinib on pain in Chinese paediatric and adult participants with NF1 and inoperable PN; to determine the effect of selumetinib on HRQoL; to determine the effect of selumetinib on physical functioning.	
PK, safety, and tolerability	D1346C00013 (Japan PK) Open-label, single-arm Phase I study designed to evaluate the safety, tolerability, PK, and efficacy of selumetinib in Japanese paediatric participants with inoperable and symptomatic NF1-related PN.	**Primary:** To evaluate the safety and tolerability of selumetinib in Japanese pediatric participants with inoperable and symptomatic NF1-related PN. **Secondary:** To evaluate plasma PK parameters of selumetinib and its metabolites (N-desmethyl selumetinib) in Japanese pediatric participants with inoperable and symptomatic NF1-related PN; to evaluate the efficacy of selumetinib on NF1-related PN by ICR volumetric MRI analysis in Japanese pediatric participants with inoperable and symptomatic NF1-related PN; to evaluate the effect of selumetinib on the PN-related morbidities (symptom and/or complications) by Investigators in Japanese pediatric participants with inoperable and symptomatic NF1-related PN; and to determine the effect of selumetinib on health-related quality of life in Japanese pediatric participants with inoperable and symptomatic NF1-related PN.	12/12
Uncontrolled clinical studies			
Efficacy and safety	D1532C00057 (SPRINT Phase II Stratum 1) Open-label (CTEP-sponsored), single-arm, multicenter study of selumetinib.	**Primary:** To evaluate the confirmed partial and complete response rate of selumetinib using volumetric MRI analysis in children and young adults with NF1 and inoperable PN with PN-related morbidity at the time of enrollment. **Secondary:** To evaluate the confirmed partial and complete response rate of selumetinib in the overall population of all participants treated (participants with and without PN-related morbidity at the time of enrollment), and those with "typical PN" versus "nodular PN" versus "solitary nodular PN"; to determine the long-term tolerability and safety of selumetinib; to determine the duration of response to selumetinib; to evaluate the effect of selumetinib on bone mineral density in participants at the NCI	50/50

Type of study	Study identifier and study design	Objective(s) of the study	No. of participants randomized/ treated
PK and safety studies			
		with impaired bone mineral density at the time of enrollment; to characterize the effect of selumetinib on pain, quality of life, and physical functioning; to determine baseline functional impairments secondary to PN, and the effect of selumetinib on functional outcomes depending on PN location; to determine the effect of selumetinib on disfigurement; to determine the effect of selumetinib on the PN growth rate based on volumetric analysis of MRI studies obtained prior to enrollment (if available and amenable to volumetric analysis); to determine TTP and PFS in progressive PN (≥ 20% increase in PN volume within 12 to 15 months prior to enrollment) and compare PFS to the placebo arm of the R115777 randomized study (01-C-0222); to determine Day 1 and steady-state PK of selumetinib; to evaluate bone marrow-derived precursor cells and cytokines pre-treatment and on treatment with selumetinib, and to assess if changes in cell and cytokine profiles correlate with imaging response to selumetinib. Additionally, in participants who enrolled in this study with presence of an optic pathway tumor or other glioma not requiring treatment with chemotherapy or radiation: To evaluate the effect of selumetinib on changes in the size of the optic pathway tumor or other glioma and to evaluate the effect of selumetinib on ERK phosphorylation in PBMC.	
Efficacy and safety	D1532C00057 (SPRINT Phase II Stratum 2) Open-label (CTEP-sponsored), single-arm, 2-strata, multicenter study of selumetinib.	To evaluate the confirmed partial and complete response rate of selumetinib; to determine the long-term tolerability and safety of selumetinib; to determine the DoR to selumetinib; and to determine PFS.	25/25
Efficacy, PK, and safety	Study D1346C00004 (SPRINKLE) Phase I/II, single-arm, open-label study to define the dosage regimen and evaluate the PK, safety, and tolerability of selumetinib given as a granule formulation.	**Primary:** To determine the PK of selumetinib after administration of the selumetinib granule formulation and to assess the safety and tolerability of the selumetinib granule formulation. Secondary: To assess the palatability of the selumetinib granule formulation and to further assess the PK of selumetinib and N-desmethyl selumetinib metabolite after administration of the selumetinib granule formulation.	38/36 (as of the clinical data cutoff 08 April 2024).

Type of study	Study identifier and study design	Objective(s) of the study	No. of participants randomized/ treated
PK and safety studies			
PK	D1532C00089 (Study 89) A Phase I, Open-label, Single-center Relative Bioavailability and Food Effect Randomized Crossover Study of New Granule and Capsule Formulations of Selumetinib (AZD6244) in Healthy Male Subjects	**Primary:** Compare the PK of the selumetinib granule formulation with selumetinib capsules in the fasted state. **Secondary:** Compare the PK of selumetinib granules when administered in the fasted state versus with a low-fat meal and evaluating the palatability of the selumetinib granule formulation	24/24
PopPK	PMX-0057.00 Report and erratum	Population Pharmacokinetic Analysis to Evaluate the Effect of Food on Selumetinib Exposure in Subjects with Neurofibromatosis type I and Plexiform	
PopPK	PMX-0116.01	Population Pharmacokinetic and Exposure-Response Analyses of Selumetinib in Patients with Neurofibromatosis type 1 (NF1) and Inoperable Plexiform (PN) in SPRINKLE Study	
	PMX-0116.01a	Population Pharmacokinetic and Exposure-Response Analyses of Selumetinib in Patients with Neurofibromatosis type 1 (NF1) and Inoperable Plexiform (PN) in SPRINKLE Study Addendum Report	

AE = adverse event; bid = twice daily; BSA = body surface area; CTEP = Cancer Therapy Evaluation Program; DoR = duration of response; GI = gastrointestinal; HRQoL = health-related quality of life; ICR = Independent Central Review; MRI = magnetic resonance imaging; MTD = maximum tolerated dose; NCI = National Cancer Institute; NF1 = Neurofibromatosis type 1; No. = number; ORR = objective response rate; PBTC = Paediatric Brain Tumor Consortium: PFS = progression-free survival; PK = pharmacokinetic(s); PN = plexiform neurofibroma(s); POB = Paediatric Oncology Branch; RP2D = Recommended Phase II dose; T1 = Treatment Period 1; T2 = Treatment Period 2; T3 = Treatment Period 3; TTR = time to response; TTP = time to progression.

2.6.2. Clinical pharmacology

Selumetinib is an orally available, selective inhibitor of mitogen activated protein kinase kinases 1 and 2 (MEK 1/2) already approved, in Europe, for the treatment as monotherapy of paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above who have symptomatic inoperable plexiform neurofibromas (PN).

The recommended paediatric dose 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 $\geq$ 1.9 m^2.

The pharmacokinetic (PK) properties of selumetinib were sufficiently characterized in the initial MAA and subsequent type II variations.

Two strengths of hard capsules, 10 and 25 mg are currently available. However, this formulation cannot be administered to children with a BSA of less than 0.55 m^2 or to young children or older patients who may struggle with swallowing capsules. The current application is to extend the marketing authorisation to include a new pharmaceutical form of selumetinib granules in capsules for

opening, 5 mg and 7.5 mg for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in patients with neurofibromatosis type 1 (NF1) aged 1 year to less than 7 years and for older patients with swallowing difficulties.

The clinical pharmacology of selumetinib granules is primarily based on a pivotal Phase 1/2 study D1346C0004 (SPRINKLE) conducted in paediatric population aged 1 to < 7 years with NF1 who received the granule formulation (rich PK data after the first dose and at steady state were available), supported by PK data from the relative BA and food effect Phase 1 study D1532C00089 (Study 89), comparing the biopharmaceutical performances of the capsule and the granule formulations in the fasted state as primary objective . This study involved a 2-part, 4-period, open-label, single-center investigation into the relative BA and food effect of a granule formulation and capsule formulation of selumetinib. The secondary objectives included comparing the PK of selumetinib granules when administered in the fasted state versus with a low-fat meal and evaluating the palatability of the selumetinib granule formulation. The study involved 24 healthy male participants aged between 18 to 45 years. It was divided into 2 study parts, with the same participants participating in both parts.

Integrated population PK analyses (Reports PMX-0116.01 and PMX-0116.01.a) combining PK data from both capsule and granule formulations were provided, along with Exposure-response analyses for safety events in the SPRINKLE study. Importantly, a request for extrapolation based on the matching systemic exposure (AUCss) approach of the efficacy outcomes from paediatric patients 3-18 years old (Sprint Study) to paediatric patients 1-3 years is agreed.

2.6.2.1. Pharmacokinetics

Absorption

Following single dose administration in healthy volunteers (Study 89), absorption of selumetinib was generally rapid in both the granule and capsule formulations. The median tmax were 1.73 hours and 1.14 hours in the fasted state and 3.03 hours and 2.00 hours in the fed state for the granules and capsules, respectively, indicating marginally slower absorption for the granule formulation.

In paediatric patients (SPRINKLE study), rapid absorption of selumetinib granules was observed, with median Tmax after single dose and at steady state was 2 to 2.5 hours post dose.

Following single dose of selumetinib granules, the geometric means of Cmax were 551 ng/mL 465 ng/mL for the global cohort 1 (≥4-<7 years old) and global cohort 2 (≥1-<4 years old), respectively. At steady state, the geometric means Cmax were 843 ng/mL 502 ng/mL for the global cohort 1 and cohort 2, respectively.

In the updated Pop-PK model (PMX-0116.01; combining both capsules and granule formulations data), the absorption of selumetinib was described by an oral bioavailability F1 of 63.8%, an absorption lag time of 0.36 hours, a duration of absorption D1 of 0.578 hours and a first-order rate constant of absorption (Ka) of 5.71 h^{-1}. Ka was dependent on formulation and is reduced for the granule formulation.

- ***Relative Bioavailability***

Study 89

This was a 2-part, 4-period open-label, single-center relative bioavailability (Part 1), and food-effect (Part 2) randomized crossover study of the selumetinib commercial capsules and an age-appropriate granule formulation in healthy volunteers (HV).

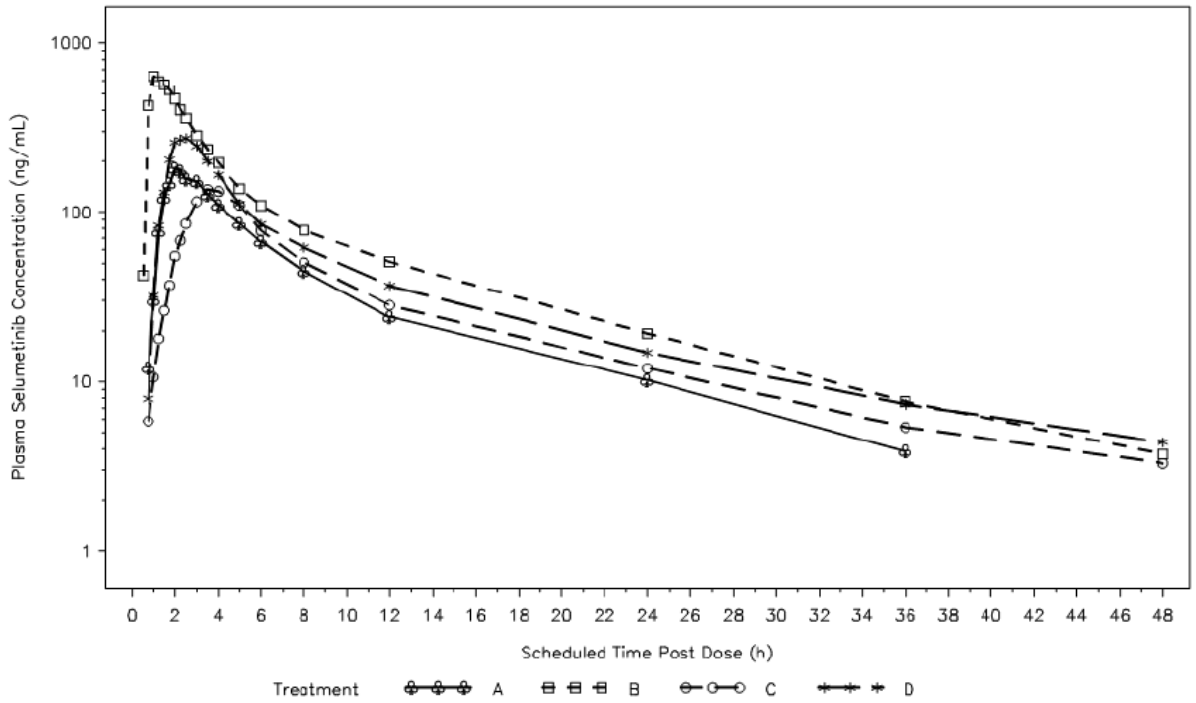
A total of 24 HV were randomized and received the treatments. The same subjects participated in both parts of the study. Each subject received the following treatments: a) Treatment A: 25 mg granule formulation, fasted state, b) Treatment B: 50 mg capsule, fasted state, c) Treatment C: 25 mg granule formulation, fed state, d) Treatment D: 50 mg capsule, fed state

The geometric mean (±gSD) selumetinib plasma concentrations versus time profiles following administration of the 25 mg granule formulation or the 50 mg capsule formulation in the fasted and fed states are presented in **Figure 3**.

Summary statistics of the key plasma selumetinib PK parameters are presented in **Table 7**.

Statistical analysis of selumetinib Cmax/D, AUC/D and AUClast/D from administration of the granule (Treatment A and C) compared to the capsule (Treatment B and D) is presented in **Table 8**.

Figure 3. Geometric Mean (± gSD) Plasma Concentration of selumetinib versus time in Study 89 (Semi-logarithmic Scale).



Treatment A: 25 mg granule, fasted state; Treatment B: 50 mg capsule, fasted state.
Treatment C: 25 mg granule, fed state; Treatment D: 50 mg capsule, fed state.

Table 7. Summary of Key plasma pharmacokinetic parameters of selumetinib in Study 89

Parameter Units	Statistic	Fasted		Fed	
		Granule 25 mg n = 24	Capsule 50 mg n = 24	Granule 25 mg n = 24	Capsule 50 mg n = 24
Cmax/D ng/mL/mg	Geomean (CV%)	13.19 (39.95)	20.17 (41.48)	7.985 (32.32)	8.084 (52.14)
AUC/D h*ng/mL/mg	Geomean (gCV%)	51.97 (26.03)	60.09 (25.29)	50.14 [a] (23.70)	37.43 (38.66)
AUClast/D h*ng/mL/mg	Geomean (gCV%)	50.05 (27.19)	58.65 (25.95)	47.19 (24.68)	35.68 (39.76)
Cmax ng/mL	Geomean (gCV%)	329.7 (39.95)	1009 (41.48)	199.6 (32.32)	404.2 (52.14)
AUC h*ng/mL	Geomean (gCV%)	1299 (26.03)	3004 (25.29)	1253 [a] (23.70)	1871 (38.66)
AUC(0-12) h*ng/mL	Geomean (gCV%)	959.4 (27.41)	2301 (29.20)	803.5 (23.20)	1287 (44.05)
AUClast h*ng/mL	Geomean (gCV%)	1251 (27.19)	2933 (25.95)	1180 (24.68)	1784 (39.76)
tmax h	Median (Min-Max)	1.73 (1.20-5.00)	1.14 (0.75-2.25)	3.03 (1.73-5.00)	2.00 (0.98-3.53)
t½λz [#] h	Arithmean (SD)	8.764 (2.349)	9.733 (2.810)	11.79 [a] (3.853)	11.91 (2.654)
CL/F L/h	Arithmean (SD)	19.86 (5.201)	17.15 (4.377)	20.47 [a] (4.751)	28.50 (10.19)
Vz/F L	Arithmean (SD)	245.7 (80.52)	243.6 (99.53)	348.5 [a] (159)	493.2 (215.8)

Table 8. Statistical Analysis of Relative Bioavailability between the granule and capsule formulation in Study 89.

Pair Granule/Capsule)	Dietary status	Parameter units	Geometric Mean@ n = 24		Pairwise Comparison@	
			Granule	Capsule	Geometric Mean Ratio	90%CI
A / B	Fasted	Cmax/D ng/mL/mg	13.19	20.17	0.654	(0.581, 0.736)
		AUC/D h*ng/mL/mg	51.97	60.09	0.865	(0.811, 0.922)
		AUClast/D h*ng/mL/mg	50.05	58.65	0.853	(0.799, 0.912)
C / D	Fed	Cmax/D ng/mL/mg	7.99	8.08	0.988	(0.819, 1.191)
		AUC/D h*ng/mL/mg	50.14	37.43	1.340	(1.171, 1.532)
		AUClast/D h*ng/mL/mg	47.19	35.68	1.323	(1.151, 1.520)

- ***Influence of food***

Based on Study 89 in HV, the median Tmax selumetinib of the granule formulation was delayed from 1.7 h in the fasted state to 3 h in the low-fat fed state.

Statistical analysis of selumetinib Cmax, AUC, AUClast, and tmax from the administration of the granule in the fed compared to the fasted state is presented in **Table 9**.

Following administration of the granule formulation in the low-fat fed state at 25 mg dose, Cmax selumetinib falls by approximately 40% compared to the fasted state, with a geometric mean Cmax ratio (90%CI) of 0.605 [0.512, 0.716]; however the overall systemic exposure on selumetinib was similar, with a geometric mean AUC ratio (90%CI) of 0.965 [0.913, 1.019].

Table 9. Statistical analysis of food effect on the granule formulation of selumetinib

Pair (Fed/Fasted)	Selumetinib Formulation	Parameter	Geometric Mean@ n=24		Pairwise Comparison@	
			Fed	Fasted	Geometric Mean Ratio	90%CI
C / A	Granule	Cmax ng/mL	199.64	329.75	0.605	(0.512, 0.716)
		AUC h*ng/mL	1253.44	1299.36	0.965	(0.913, 1.019)
		AUClast h*ng/mL	1179.65	1251.20	0.943	(0.890, 0.999)
		tmax h	3.21	1.84	1.750	(1.515, 2.022)

Distribution

Following administration of selumetinib granules at nominal 25 mg/m^2 dose in paediatric patients with NF1 aged 1-<7 years old (SPRINKLE study), the geometric mean (gCV%) apparent volume of distribution after single dose (Vz/F) and volume of distribution at steady state (Vss/F) of selumetinib were 75.3 L (44%) and 32 (48%) L, with values ranging from 28 to 178 L and from 13 to 68 L, respectively, indicating moderate distribution into tissue.

Elimination

Following single dose of selumetinib granules at nominal 25 mg/m2 dose in paediatric patients with NF1 aged 1-<7 years old, the geometric mean apparent oral clearance (CL/F) was 7.1 L/hr (gCV% = 34%) and mean elimination half-life was 7.4 hours (gCV% =50%).

Dose proportionality and time dependencies

No new data regarding dose proportionality are provided. Only one single dose level was tested in the dedicated paediatric SPRINKLE study, equivalent to 25 mg/m^2.

Based on data collected after single dose (Cycle 1 day 1) and at steady state (C2D1), the accumulation was 1.46 and 1.3-fold for AUC0-12h and Cmax, respectively following repeated BID administration of the selumetinib granule formulation.

Pharmacokinetics in the paediatric population

The PKs of selumetinib and its active metabolite N-desmethyl selumetinib in paediatric patients with NF1 aged 1 to < 7 years was evaluated within a dedicated Phase 1/2 study (SPRINKLE)**.** Rich PK data after the single dose (C1D1) and at steady-state after repeated administration (C2D1) were collected.

PK data provided in the current submission and discussed in this report are based on a cut-off date (DCO) of 08 Apr 2024 (when all patients had the opportunity to complete 3 cycles of treatment).

SPRINKLE study

This is an ongoing single-arm, open-label study to evaluate the PKs, safety and efficacy of selumetinib given as a granule formulation at a dose equivalent to 25 mg/m2 (based on BSA) BID to children aged ≥ 1 to < 7 years with NF1 related symptomatic, inoperable PN. Patients are receiving selumetinib for 25 cycles (or until they meet discontinuation criteria). Each treatment cycle spans 28 days.

Patients were required to have a BSA within the range 0.40 to 1.09 m^2 at enrolment.

Patients who attain a BSA between 1.10 and 1.29 m^2 and complete at least 3 cycles of treatment with the granule formulation are encouraged to transition to the capsule formulation, if feasible.

A total of n = 36 patients received treatment: 15 patients in the global cohort 1 [≥ 4 to < 7 years], 17 patients in global cohort 2 [≥ 1 to < 4 years], and 4 patients in the Japan cohort [1 patient ≥ 1 to < 4 years and 3 participants ≥ 4 to < 7 years]).

The selumetinib granule formulation dose schema is shown in **Table 10**.

Table 10. Proposed Selumetinib Granule Formulation Dose Schema in Paediatrics

BSA (m^2)	Granules Dose (bid approximately 12 hours apart)	Dose level (mg/m^2)
0.40 - 0.49	10 mg	20.4 – 25.0
0.50 - 0.59	12.5 mg	21.2 – 25.0
0.60 - 0.69	15 mg	21.7 – 25.0
0.70 - 0.89	20 mg	22.5 - 28.9
0.90 - 1.09	25 mg	22.9 - 27.8
1.10 - 1.29 [a]	30 mg	23.3 - 27.3

PK evaluation: the plasma PK of selumetinib and its active metabolite N-desmethyl selumetinib were sampled after the first selumetinib dose in Cycle 1 (C1D1). Blood samples were obtained immediately before the first selumetinib administration, and 1, 2, 3, 4, 6, 8, 10 to 12, and 18 to 24 hours post dose. Steady-state PK parameters were estimated from samples collected predose and 1, 2, 3, 4, 6, 8, 10 to 12 hours following the morning dose on Cycle 2 Day 1 (C2D1).

Results

Selumetinib plasma concentrations in the global cohorts

The geometric mean plasma concentration vs. time profiles of selumetinib in paediatric patients aged 1-7 years following the first dose (C1D1) and at steady state (C2D1) are shown in **Figure 4** and **Figure 5**, respectively.

Selumetinib selumetinib PK parameters in pediatric patients after single and repeated doses are presented in **Table 11** and **Table 12**, respectively.

Figure 4. Geometric Mean Selumetinib Plasma Concentration Versus Time after single dose administration C1D1, Granule Formulation, Global Cohorts of SPRINKLE study

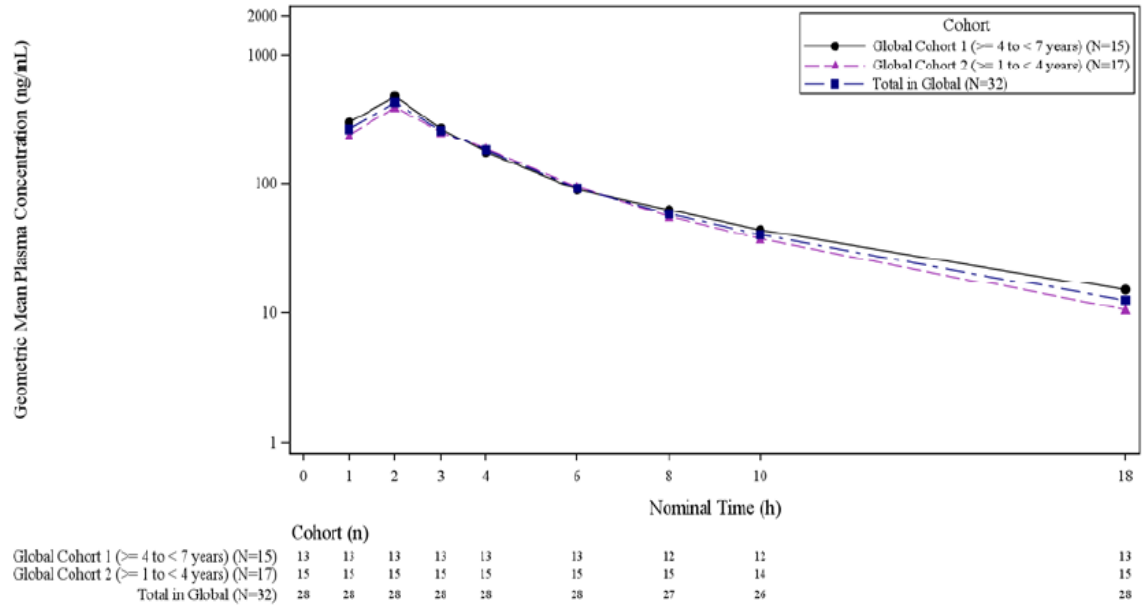


Figure 5. Geometric Mean Selumetinib Plasma Concentration Versus Time at C2D1, Granule Formulation, Global Cohorts of SPRINKLE study (linear scale)

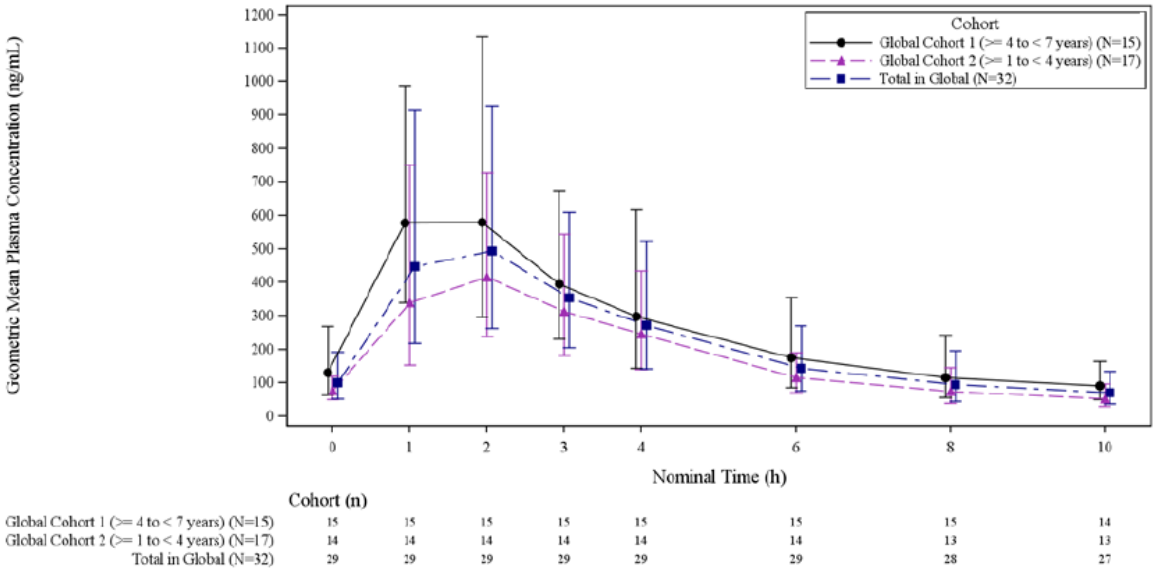


Table 11. Summary of Single-Dose Selumetinib Pharmacokinetic Parameters Following Oral administration of Granule Formulation in Cycle 1, Day 1, Global Cohorts of SPRINKLE study

Parameter (units)	Statistic	Cohort 1 ≥ 4 to < 7 years	Cohort 2 ≥ 1 to < 4 years	Total in Global
C_{max} (ng/mL)	Gmean (gCV%) Min-max [n]	551.1 (44.21%) 247 - 1300 [13]	464.7 (54.05%) 225 - 1130 [15]	503.0 (49.58%) 225 - 1300 [28]
t_{max} (h)	Median Min-max [n]	1.83 0.83 - 2.98 [13]	2.00 1.00 - 3.88 [15]	1.97 0.83 - 3.88 [28]
t_{last} (h)	Median Min-max [n]	23.10 21.58 - 24.00 [13]	23.25 22.17 - 24.00 [15]	23.20 21.58 - 24.00 [28]
AUC_{0-6} (h*ng/mL)	Gmean (gCV%) Min-max [n]	1516 (30.42%) 841 - 3000 [13]	1352 (37.13%) 808 - 2630 [15]	1426 (34.05%) 808 - 3000 [28]
AUC_{0-12} (h*ng/mL)	Gmean (gCV%) Min-max [n]	1902 (24.19%) 1480 - 3520 [13]	1699 (31.02%) 1040 - 2970 [15]	1790 (28.15%) 1040 - 3520 [28]
AUC_{0-24} (h*ng/mL)	Gmean (gCV%) Min-max [n]	2222 (24.72%) 1680 - 4150 [13]	1942 (29.73%) 1160 - 3220 [15]	2067 (27.91%) 1160 - 4150 [28]
AUC_{last} (h*ng/mL)	Gmean (gCV%) Min-max [n]	2208 (24.81%) 1670 - 4150 [13]	1932 (29.59%) 1160 - 3190 [15]	2055 (27.85%) 1160 - 4150 [28]
CL/F (L/h)	Gmean (gCV%) Min-max [n]	8.411 (19.66%) 5.95 - 10.9 [12]	6.167 (36.79%) 2.62 - 10.4 [15]	7.079 (33.95%) 2.62 - 10.9 [27]
Vz/F (L)	Gmean (gCV%) Min-max [n]	91.63 (33.64%) 56.5 - 178 [12]	64.33 (44.81%) 28.6 - 142 [15]	75.28 (43.86%) 28.6 - 178 [27]
$t_{½\lambda z}$ (h)	Gmean (gCV%) Min-max [n]	7.551 (41.21%) 4.28 - 15.0 [12]	7.230 (58.00%) 4.33 - 37.6 [15]	7.371 (49.98%) 4.28 - 37.6 [27]

Table 12. Summary of Multiple-Dose Selumetinib Pharmacokinetic Parameters Following Oral Administration of Granule Formulation in Cycle 2, Day 1, Global Cohorts of SPRINKLE study

Parameter (units)	Statistic	Cohort 1 ≥ 4 to < 7 years	Cohort 2 ≥ 1 to < 4 years	Total in Global
C_{max} (ng/mL)	Gmean (gCV%) Min-max [n]	843.4 (42.69%) 428 - 1590 [15]	502.6 (58.59%) 184 - 1310 [14]	656.9 (58.01%) 184 - 1590 [29]
t_{max} (h)	Median Min-max [n]	2.00 0.92 - 4.07 [15]	1.97 0.92 - 4.05 [14]	2.00 0.92 - 4.07 [29]
t_{last} (h)	Median Min-max [n]	10.00 8.03 - 12.00 [15]	10.00 9.58 - 12.00 [14]	10.00 8.03 - 12.00 [29]
AUC_{0-6} (h*ng/mL)	Gmean (gCV%) Min-max [n]	2412 (43.55%) 1350 - 6310 [15]	1672 (48.14%) 701 - 2800 [14]	2021 (49.40%) 701 - 6310 [29]
AUC_{0-12} (h*ng/mL)	Gmean (gCV%) Min-max [n]	3095 (47.81%) 1570 - 8290 [15]	2114 (49.23%) 888 - 3750 [14]	2575 (52.23%) 888 - 8290 [29]
AUC_{last} (h*ng/mL)	Gmean (gCV%) Min-max [n]	2919 (48.28%) 1500 - 7870 [15]	2031 (49.45%) 847 - 3550 [14]	2450 (52.12%) 847 - 7870 [29]
CL/F (L/h)	Gmean (gCV%) Min-max [n]	6.166 (50.01%) 2.41 - 10.8 [15]	6.051 (48.38%) 3.33 - 14.1 [14]	6.110 (48.25%) 2.41 - 14.1 [29]
V_{ss}/F (L)	Gmean (gCV%) Min-max [n]	33.71 (44.31%) 12.9 - 53.5 [15]	30.05 (52.48%) 15.1 - 67.7 [13]	31.96 (47.63%) 12.9 - 67.7 [28]
$RacC_{max}$	Gmean (gCV%) Min-max [n]	1.508 (56.59%) 0.607 - 4.09 [15]	1.104 (92.61%) 0.173 - 3.33 [13]	1.304 (74.80%) 0.173 - 4.09 [28]
$RacAUC_{0-12}$	Gmean (gCV%) Min-max [n]	1.641 (54.51%) 0.696 - 4.91 [14]	1.289 (61.20%) 0.314 - 2.63 [13]	1.461 (58.23%) 0.314 - 4.91 [27]

A comparison between observed PK parameters after a single dose of selumetinib in paediatric patients aged 1-<7 years old (granule formulation) and those from the reference paediatric population aged [3-18] years (SPRINT study, capsule formulation) is presented in **Table 13**.

Table 13. Selumetinib PK Parameters in Paediatric patients after Single Dose

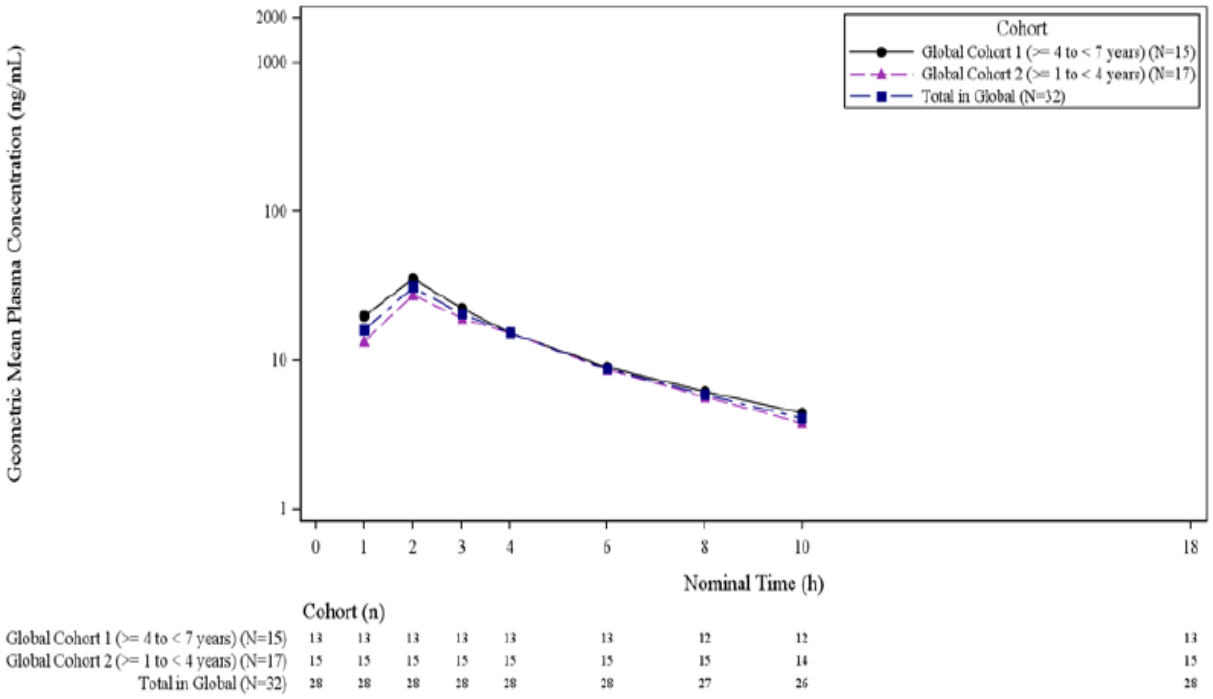
	Dose (mg/m^2)	N[a]	C_{max} (ng/mL) (gCV%)[b]	t_{max} (h) (range)[c]	AUC[d] (ng × h/mL) (gCV%)[b] [min-max]
SPRINT (Phase II Stratum I, selumetinib capsules in pediatric participants aged ≥ 3 years)	25	50	731 (62)	1.5 (0.5-6)	2009 (35.24) [855, 4560]
SPRINKLE (selumetinib granules in pediatric participants aged ≥ 4 to < 7 years), Global Cohort 1	25	13	551.1 (44.21)	1.83 (0.83-2.98)	1902 (24.19) [1480, 3520]
SPRINKLE (selumetinib granules in pediatric participants aged ≥1 to < 4 years), Global Cohort 2	25	15	464.7 (54.05)	2.00 (1.00-3.88)	1699 (31.02) [1040, 2970]
SPRINKLE (selumetinib granules in pediatric participants aged ≥1 to < 7 years), Total in Global Cohort	25	28	503.0 (49.58)	1.97 (0.83-3.88)	1790 (28.15) [1040, 3520]

N-desmethyl selumetinib plasma concentrations in the global cohorts

The geometric mean plasma concentration vs. time profiles of N-desmethyl selumetinib in paediatric patients with NF1 aged 1-<7 years following the first dose (C1D1) and at steady state (C2D1) are shown in **Figure 6** and **Figure** 7, respectively.

N-desmethyl selumetinib PK parameters in pediatric patients after single and repeated doses are presented in **Table 14** and **Table 15**, respectively.

Figure 6. Geometric Mean N-Desmethyl Selumetinib Plasma Concentration Versus Time at Cycle 1, Day 1, Granule Formulation, Global Cohorts in SPRINKLE study



Cohort (n)									
Global Cohort 1 (>= 4 to < 7 years) (N=15)	13	13	13	13	13	13	12	12	13
Global Cohort 2 (>= 1 to < 4 years) (N=17)	15	15	15	15	15	15	15	14	15
Total in Global (N=32)	28	28	28	28	28	28	27	26	28

Table 14. Summary of N-Desmethyl Selumetinib Pharmacokinetic Parameters Following Oral Administration of Granule Formulation in C1D1, Global Cohorts of SPRINKLE study

Parameter (units)	Statistic	Cohort 1 ≥ 4 to < 7 years	Cohort 2 ≥ 1 to < 4 years	Total in Global
C_{max} (ng/mL)	Gmean (gCV%) Min-max [n]	40.53 (45.76%) 16.7 - 109 [13]	32.73 (52.62%) 14.8 - 92.9 [15]	36.14 (49.99%) 14.8 - 109 [28]
t_{max} (h)	Median Min-max [n]	1.83 0.83 - 2.98 [13]	2.02 1.00 - 5.87 [15]	2.00 0.83 - 5.87 [28]
t_{last} (h)	Median Min-max [n]	10.12 10.00 - 24.00 [13]	10.02 7.65 - 22.67 [15]	10.03 7.65 - 24.00 [28]
AUC_{0-6} (h*ng/mL)	Gmean (gCV%) Min-max [n]	118.3 (31.40%) 63.3 - 258 [13]	99.73 (36.98%) 50.6 - 169 [15]	108.0 (35.04%) 50.6 - 258 [28]
AUC_{0-12} (h*ng/mL)	Gmean (gSD%) Min-max [n]	156.1 (25.76%) 116 - 318 [13]	134.0 (34.21%) 71.2 - 202 [13]	144.6 (30.69%) 71.2 - 318 [26]
AUC_{0-24} (h*ng/mL)	Gmean (gCV%) Min-max [n]	182.4 (27.93%) 139 - 382 [13]	148.3 (37.04%) 76.4 - 213 [13]	164.5 (33.92%) 76.4 - 382 [26]
AUC_{last} (h*ng/mL)	Gmean (gCV%) Min-max [n]	167.7 (32.98%) 130 - 382 [13]	129.7 (38.46%) 61.7 - 208 [15]	146.2 (37.93%) 61.7 - 382 [28]
t½λz (h)	Gmean (gCV%) Min-max [n]	5.198 (79.02%) 2.07 - 15.6 [13]	3.912 (94.73%) 1.54 - 35.7 [13]	4.509 (86.77%) 1.54 - 35.7 [26]
$MPAUC_{0-6}$	Gmean (gCV%) Min-max [n]	0.07803 (18.27%) 0.0601 - 0.120 [13]	0.07379 (15.50%) 0.0561 - 0.0981 [15]	0.07573 (16.76%) 0.0561 - 0.120 [28]
$MPAUC_{0-12}$	Gmean (gCV%) Min-max [n]	0.08204 (17.91%) 0.0627 - 0.125 [13]	0.07722 (17.19%) 0.0588 - 0.101 [13]	0.07960 (17.48%) 0.0588 - 0.125 [26]
$MPAUC_{0-24}$	Gmean (gCV%) Min-max [n]	0.08209 (19.94%) 0.0573 - 0.131 [13]	0.07516 (18.93%) 0.0573 - 0.0996 [13]	0.07855 (19.59%) 0.0573 - 0.131 [26]
MPC_{max}	Gmean (gCV%) Min-max [n]	0.07353 (20.68%) 0.0516 - 0.120 [13]	0.07044 (17.43%) 0.0534 - 0.0942 [15]	0.07186 (18.76%) 0.0516 - 0.120 [28]

Figure 7. Geometric Mean N-Desmethyl Selumetinib Plasma Concentration Versus Time at Cycle 1, Day 1, Granule Formulation, Global Cohorts in SPRINKLE study

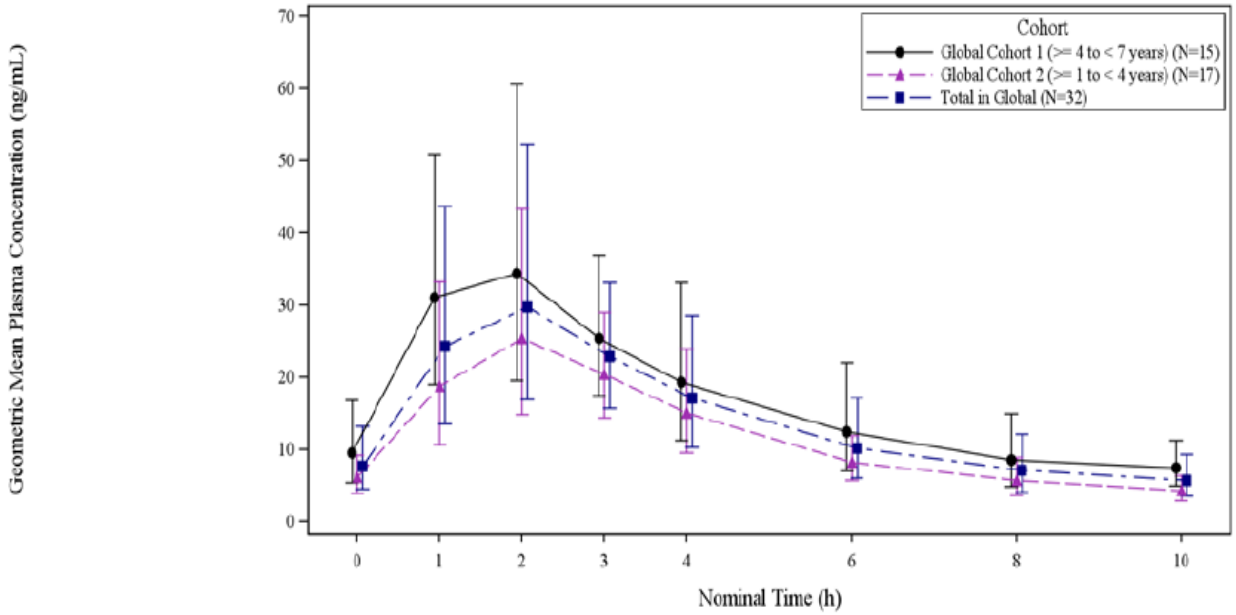


Table 15. Summary of N-Desmethyl Selumetinib Pharmacokinetic Parameters Following multiple oral doses of Granule Formulation in C2D1, global cohorts of SPRINKLE study

Parameter (units)	Statistic	Cohort 1 ≥ 4 to < 7 years	Cohort 2 ≥ 1 to < 4 years	Total in Global
C_{max} (ng/mL)	Gmean (gCV%) Min-max [n]	47.53 (38.92%) 29.9 - 99.8 [15]	29.12 (47.81%) 13.6 - 59.3 [14]	37.52 (50.63%) 13.6 - 99.8 [29]
t_{max} (h)	Median Min-max [n]	2.00 0.92 - 4.07 [15]	2.01 0.92 - 4.05 [14]	2.00 0.92 - 4.07 [29]
t_{last} (h)	Median Min-max [n]	10.00 8.03 - 12.00 [15]	10.00 9.58 - 12.00 [14]	10.00 8.03 - 12.00 [29]
AUC_{0-6} (h*ng/mL)	Gmean (gCV%) Min-max [n]	145.6 (31.30%) 73.6 - 229 [15]	102.4 (35.17%) 53.0 - 191 [14]	122.8 (37.71%) 53.0 - 229 [29]
AUC_{0-12} (h*ng/mL)	Gmean (gCV%) Min-max [n]	192.9 (33.37%) 88.9 - 311 [14]	135.9 (33.82%) 73.5 - 227 [14]	161.9 (37.97%) 73.5 - 311 [28]
AUC_{last} (h*ng/mL)	Gmean (gCV%) Min-max [n]	183.4 (34.54%) 83.9 - 292 [15]	128.9 (34.30%) 68.8 - 218 [14]	154.7 (38.80%) 68.8 - 292 [29]
$MPAUC_{0-6}$	Gmean (gCV%) Min-max [n]	0.06036 (29.62%) 0.0359 - 0.0993 [15]	0.06123 (26.61%) 0.0368 - 0.0817 [14]	0.06078 (27.69%) 0.0359 - 0.0993 [29]
$MPAUC_{0-12}$	Gmean (gCV%) Min-max [n]	0.06413 (29.74%) 0.0376 - 0.102 [14]	0.06429 (26.09%) 0.0387 - 0.0869 [14]	0.06421 (27.42%) 0.0376 - 0.102 [28]
MPC_{max}	Gmean (gCV%) Min-max [n]	0.05635 (38.03%) 0.0323 - 0.0987 [15]	0.05794 (26.08%) 0.0361 - 0.0806 [14]	0.05711 (32.14%) 0.0323 - 0.0987 [29]
$RacC_{max}$	Gmean (gCV%) Min-max [n]	1.142 (61.34%) 0.481 - 3.36 [15]	0.8837 (76.53%) 0.224 - 2.79 [13]	1.014 (68.79%) 0.224 - 3.36 [28]
$RacAUC_{0-12}$	Gmean (gCV%) Min-max [n]	1.221 (35.39%) 0.575 - 2.15 [13]	1.099 (53.72%) 0.441 - 2.83 [11]	1.163 (43.69%) 0.441 - 2.83 [24]

Population PK analysis (PMX-0116.01)

Additional to formal NCA calculations, a new Pop-PK analysis was performed updating the original Pop-PK analysis (Report PMX-0057.00).

Plasma concentration-time data were analysed using a non-linear mixed effects modelling approach performed using NONMEM with a qualified installation of the software, version 7.3.0 (ICON Development Solutions, Hanover, MD). Visual predictive check (VPC) and simulations were performed using NONMEM with a qualified installation of the software, version 7.4.3.

Graphical exploration of data, pre- and post-processing of results as well as logistic regression analyses for safety were performed using R, v4.2.2. Dataset assembly was performed using SAS v9.4 (SAS Institute, Cary, NC).

Individual vs. observed concentration-time profiles were derived using Xpose (version 0.4.16).

Model evaluation was based on standard model diagnostics and goodness-of-fit criteria (i.e., accuracy of parameter estimation [i.e., 95% confidence interval excluding 0], successful model convergence) and by looking at pertinent graphical representations of goodness-of-fit (i.e., fitted and observed concentrations versus time, weighted residuals vs. time). Model validation/qualification of population PK models was based on the DV vs. PRED, DV vs. IPRED CWRES vs. PRED CWRES vs. time and QQ plot diagnostic plots

The performance of the models was evaluated using several methods including diagnostic plots, as well as Prediction-corrected VPC (pcVPC) plots.

PK dataset

New PK data from 3 clinical studies: Study 11 (n= 32 Chinese paediatric and adult patients), Study 13 (n = 12 Japanese paediatric patients,) and from the pivotal SPRINKLE study in patients aged 1-<7 years with NF1 who received the new granule formulation (n = 36; n = 32 in the global cohort and n = 4 in the Japan cohort) were added to the previous PK dataset collected from 15 studies (including the pivotal SPRINT study in n= 68 paediatric patients with NF1aged [3-18] years old).

The final population dataset included 10412 plasma selumetinib, 217 radioactive C14 compound and 8601 plasma N-desmethyl selumetinib concentrations available from 591 subjects across 18 studies.

Descriptive statistics of baseline characteristics are presented in **Table 16** and **Table 17** for the overall modeling dataset. The median age (range) and BSA (range) in the overall population were 26.0 years and 1.82 m2, respectively. The population included a total of 120 (20.3%) female and 471 (79.7%) male subjects.

Table 16. Descriptive Statistics – Baseline Characteristics – Overall Population

Demographic	Pediatric (≥1 to <3 years) (N=13)	Pediatric (≥3 to <7 years) (N=43)	Pediatric (≥7 to ≤18 years) (N=103)	Adult (>18 years) (N=432)	Overall (N=591)
Age (year)					
Mean (SD)		4.86 (1.18)	12.8 (3.20)	36.3 (14.4)	29.2 (17.2)
Median [Min, Max]		5.00 [3.00, 6.90]	13.0 [7.00, 18.0]	32.0 [18.2, 79.0]	26.0 [, 79.0]
Percentile [5th, 95th]		[3.00, 6.40]	[7.42, 17.9]	[20.0, 64.0]	[4.00, 63.0]
Sex					
Female	6 (46.2%)	20 (46.5%)	46 (44.7%)	48 (11.1%)	120 (20.3%)
Male	7 (53.8%)	23 (53.5%)	57 (55.3%)	384 (88.9%)	471 (79.7%)
Race					
White	10 (76.9%)	28 (65.1%)	63 (61.2%)	230 (53.2%)	331 (56.0%)
Black	0 (0%)	1 (2.3%)	6 (5.8%)	109 (25.2%)	116 (19.6%)
Asian-Chinese	0 (0%)	2 (4.7%)	17 (16.5%)	20 (4.6%)	39 (6.6%)
Asian-Japanese	1 (7.7%)	3 (7.0%)	11 (10.7%)	28 (6.5%)	43 (7.3%)
Asian-Indian	0 (0%)	0 (0%)	0 (0%)	10 (2.3%)	10 (1.7%)
Asian-Other	0 (0%)	2 (4.7%)	3 (2.9%)	30 (6.9%)	35 (5.9%)
Any others	1 (7.7%)	3 (7.0%)	0 (0%)	5 (1.2%)	9 (1.5%)
Missing/Not reported	1 (7.7%)	4 (9.3%)	3 (2.9%)	0 (0%)	8 (1.4%)
Body Weight (kg)					
Mean (SD)	11.8 (1.39)	19.0 (3.94)	43.9 (17.7)	75.3 (12.5)	64.4 (23.3)
Median [Min, Max]	12.0 [ ]	18.4 [ ]	42.8 [ ]	76.2 [ ]	70.0 [ ]
Percentile [5th, 95th]	[9.50, 13.6]	[14.4, 24.8]	[21.0, 81.9]	[54.5, 94.5]	[16.8, 92.2]
BSA (m²)					
Mean (SD)	0.522 (0.0509)	0.745 (0.0966)	1.34 (0.338)	1.89 (0.183)	1.68 (0.439)
Median [Min, Max]	0.530 [ ]	0.751 [ ]	1.36 [ ]	1.92 [ ]	1.82 [ ]
Percentile [5th, 95th]	[0.432, 0.584]	[0.630, 0.883]	[0.836, 1.93]	[1.58, 2.17]	[0.693, 2.15]
Subject type					
Patient	13 (100%)	43 (100%)	101 (98.1%)	100 (23.1%)	257 (43.5%)
Healthy	0 (0%)	0 (0%)	2 (1.9%)	332 (76.9%)	334 (56.5%)

Personal data removed from the table

Table 17. Descriptive Statistics – Baseline Markers of liver/renal function – Overall Population

Demographic	Pediatric (≥1 to <3 years) (N=13)	Pediatric (≥3 to <7 years) (N=43)	Pediatric (≥7 to ≤18 years) (N=103)	Adult (>18 years) (N=432)	Overall (N=591)
Albumin (g/L)					
Mean (SD)	42.8 (4.92)	42.1 (2.63)	44.2 (3.69)	42.1 (5.45)	42.5 (5.07)
Median [Min, Max]	43.0 [31.0, 50.0]	41.8 [37.0, 49.0]	44.0 [35.0, 55.0]	43.0 [20.0, 55.0]	43.0 [20.0, 55.0]
Percentile [5th, 95th]	[35.4, 48.5]	[38.0, 45.5]	[38.0, 49.9]	[31.0, 49.0]	[33.2, 49.0]
Missing	2 (15.4%)	1 (2.3%)	0 (0%)	1 (0.2%)	4 (0.7%)
ALP (U/L)					
Mean (SD)	186 (41.9)	176 (39.5)	185 (148)	91.9 (107)	116 (118)
Median [Min, Max]	190 [119, 281]	172 [124, 280]	145 [51.0, 881]	68.0 [36.0, 1330]	79.0 [36.0, 1330]
Percentile [5th, 95th]	[123, 244]	[127, 244]	[75.1, 553]	[44.0, 204]	[46.0, 257]
ALT (µkat/L)					
Mean (SD)	0.324 (0.144)	0.298 (0.155)	0.250 (0.108)	0.417 (0.186)	0.377 (0.184)
Median [Min, Max]	0.283 [0.100, 0.600]	0.283 [0.100, 1.00]	0.233 [0.0830, 0.767]	0.383 [0.100, 1.23]	0.350 [0.0830, 1.23]
Percentile [5th, 95th]	[0.150, 0.550]	[0.135, 0.545]	[0.133, 0.430]	[0.183, 0.748]	[0.150, 0.699]
AST (µkat/L)					
Mean (SD)	0.555 (0.0870)	0.492 (0.243)	0.331 (0.161)	0.408 (0.181)	0.404 (0.187)
Median [Min, Max]	0.567 [0.383, 0.700]	0.433 [0.267, 1.90]	0.300 [0.117, 1.48]	0.383 [0.133, 1.84]	0.367 [0.117, 1.90]
Percentile [5th, 95th]	[0.433, 0.670]	[0.335, 0.710]	[0.189, 0.576]	[0.232, 0.707]	[0.217, 0.700]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.2%)
Bilirubin (mg/dL)					
Mean (SD)	0.330 (0.146)	0.431 (0.188)	0.563 (0.365)	0.650 (0.290)	0.612 (0.305)
Median [Min, Max]	0.300 [0.160, 0.600]	0.410 [0.200, 1.13]	0.513 [0.205, 3.15]	0.600 [0.158, 2.87]	0.580 [0.158, 3.15]
Percentile [5th, 95th]	[0.184, 0.600]	[0.200, 0.717]	[0.205, 1.15]	[0.300, 1.18]	[0.265, 1.17]
Missing	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	1 (0.2%)
Serum Creatinine (mg/dL)					
Mean (SD)	0.275 (0.0789)	0.343 (0.0805)	0.512 (0.171)	0.925 (0.175)	0.796 (0.274)
Median [Min, Max]	0.290 [0.150, 0.400]	0.330 [0.200, 0.599]	0.500 [0.200, 0.950]	0.913 [0.464, 1.55]	0.860 [0.150, 1.55]
Percentile [5th, 95th]	[0.156, 0.376]	[0.260, 0.479]	[0.272, 0.789]	[0.628, 1.20]	[0.300, 1.20]
Creatinine Clearance (mL/min/1.73m²)					
Mean (SD)	173 (41.6)	205 (48.2)	191 (56.5)	108 (24.0)	131 (51.4)
Median [Min, Max]	170 [110, 251]	198 [131, 327]	183 [100, 418]	107 [40.0, 192]	116 [40.0, 418]
Percentile [5th, 95th]	[113, 235]	[136, 285]	[124, 277]	[68.6, 150]	[72.2, 237]

Final model / Qualification

Population PK parameters derived with the full model are summarised in **.**

Table 18.

The goodness-of-fit for selumetinib and N-desmethyl selumetinib derived with the final population PK model for the overall data are presented in **Figure 8** and **Figure 9**.

The goodness-of-fit of selumetinib for SPRINKLE study, granule formulation and age groups [1-3] and [3-7] years old are presented in **Figure 10**, **Figure 11** and **Figure 12**, respectively.

Results of the prediction-corrected VPC for selumetinib and N-desmethyl selumetinib are presented on semi-log scale in **Figure 13** and **Figure 14**, respectively. The pcVPC of selumetinib by formulation (capsule versus granule formulations) is presented in **Figure 15** .

The pcVPC of selumetinib for the specific Sprinkle study and by age groups of interest ([1-3] and [3-7] years) could not be found / are not provided.

Table 18. Parameter estimates for the final selumetinib population PK model

Parameter	Estimate	RSE%	95% CI	Shrinkage
Selumetinib				
F1 (logit)	0.565	21.5	0.327, 0.803	NA
ALAG1 (h)	0.360	2.15	0.345, 0.376	NA
D1 (h)	0.578	1.67	0.559, 0.597	NA
Ka (1/h)	5.71	13.2	4.23, 7.20	NA
CL (L/h)	10.9	4.46	9.93, 11.8	NA
V2 (L)	29.7	5.27	26.6, 32.8	NA
Q (L/h)	7.44	4.41	6.79, 8.08	NA
V3 (L)	51.0	4.76	46.3, 55.8	NA
N-Desmethyl Selumetinib				
Fm (logit)	-1.91	3.49	-2.05, -1.78	NA
CLm (L/h)	16.3	5.27	14.6, 18.0	NA
Covariate Effects				
Low fat meal on F1	-0.718	6.26	-0.806, -0.630	NA
High fat meal on F1	-0.417	10.7	-0.504, -0.330	NA
Without regard to food on F1*	0.420	35.9	0.125, 0.715	NA
Low fat meal on D1	1.50	1.12	1.47, 1.53	NA
High fat meal on D1	1.20	2.30	1.15, 1.26	NA
Without regard to food on D1*	0.307	36.5	0.0878, 0.527	NA
Low fat meal on Ka^	0.165	10.6	0.130, 0.199	NA
High fat meal on Ka^	-2.78	2.04	-2.89, -2.67	NA
Granule on Ka	-2.72	1.55	-2.80, -2.64	NA
Health Status on Ka	0.839	18.0	0.544, 1.13	NA
Age on clearances	-0.0744	28.9	-0.117, -0.0322	NA
BSA on clearances	0.900	6.45	0.786, 1.01	NA
Race (Asian) on CL	-0.134	18.1	-0.181, -0.0861	NA
BSA on V2	1.65	7.38	1.41, 1.88	NA
BSA on V3	0.474	11.1	0.371, 0.577	NA
BSA on Fm	-1.13	5.60	-1.25, -1.00	NA
BALB on Fm	1.09	8.93	0.902, 1.29	NA
Between-Subject Variability[a]				
On $ALAG_1$	0.391 (40.6)	3.30	0.365, 0.416	12.1%
On Ka	1.57 (331)	4.52	1.44, 1.71	18.2%
On CL	0.235 (23.9)	3.59	0.219, 0.252	12.4%
On V2	0.415 (43.4)	3.93	0.384, 0.447	22.7%
On V3	0.351 (36.3)	4.54	0.320, 0.383	26.3%
On Fm	0.379 (39.3)	2.77	0.358, 0.400	6.85%
Correlation CL, V2	0.609	6.51	0.531, 0.687	NA
Residual Error				
Selumetinib additive error (log(nmol/L))	0.505	0.378	0.502 – 0.509	NA
N-desmethyl selumetinib additive error (log(nmol/L))	0.402	0.494	0.398 – 0.405	NA
[14C]-selumetinib additive error (log(nmol/L))	0.416	2.60	0.395 – 0.437	NA

Abbreviations: F1 = bioavailability; ALAG1 = Absorption lag time; D1 = duration of the zero-order absorption rate; Ka = first-order absorption rate constant; CL = selumetinib clearance; V2 = selumetinib central volume; Q = selumetinib intercompartmental clearance; V3 = selumetinib peripheral volume; Fm = fraction metabolized to N-desmethyl selumetinib; CLm = N-desmethyl selumetinib plasma clearance; BSV = between-subject variability; RSE = relative standard error; NA = not applicable.

a. Between-subject variability is presented as the omega (ω) value with the % coefficient of variation presented in parentheses (100 x (exp(ω2)-1)$^{0.5}$).

Note 1: The reference is a non-Asian patient of 29 years with a BSA of 1.8 m^2 who received selumetinib under fasting conditions.

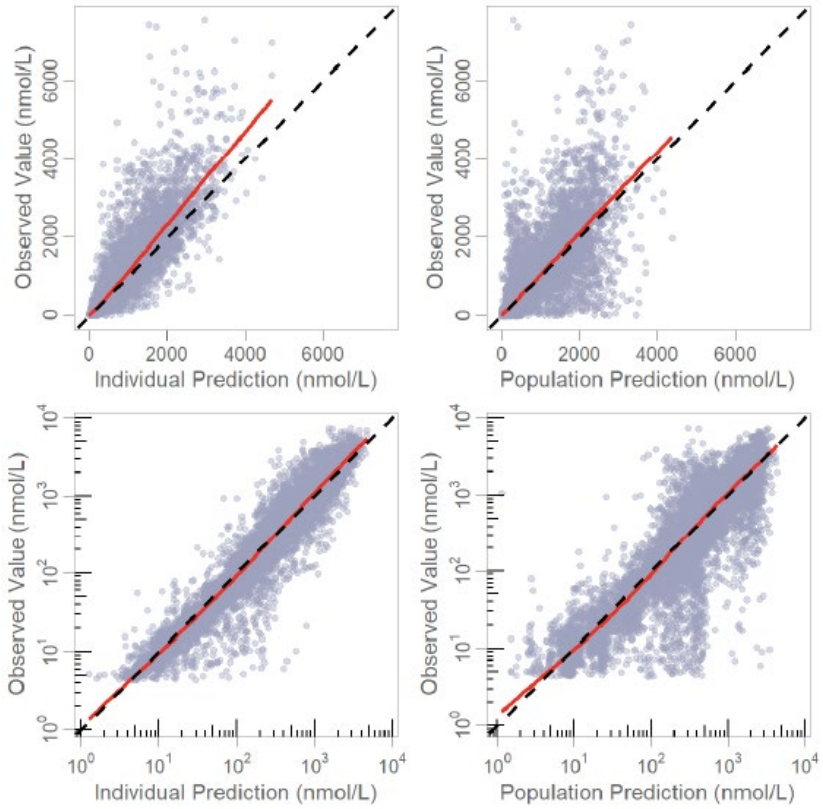
Note 2: the F1 and Fm were estimated using a logit function to restrict the estimated value between 0 and 1. The resulting F1 is 63.8% [i.e., exp$^{0.565}$/ (exp$^{0.565}$ + 1)]. The resulting Fm is 12.9% [i.e., exp$^{-1.91}$/ (exp$^{-1.91}$ + 1)].

** Drug administration "Without regard to food" is only applicable in Cohort 2 of in the SPRINKLE Study.*

^ Effect of "without regard to food" on Ka was lumped with the fasting condition in the final model.

Objective function value: -14534.59. Condition number: 815.7253.

Figure 8. Final Population PK Model of Selumetinib: Goodness-of-Fit.



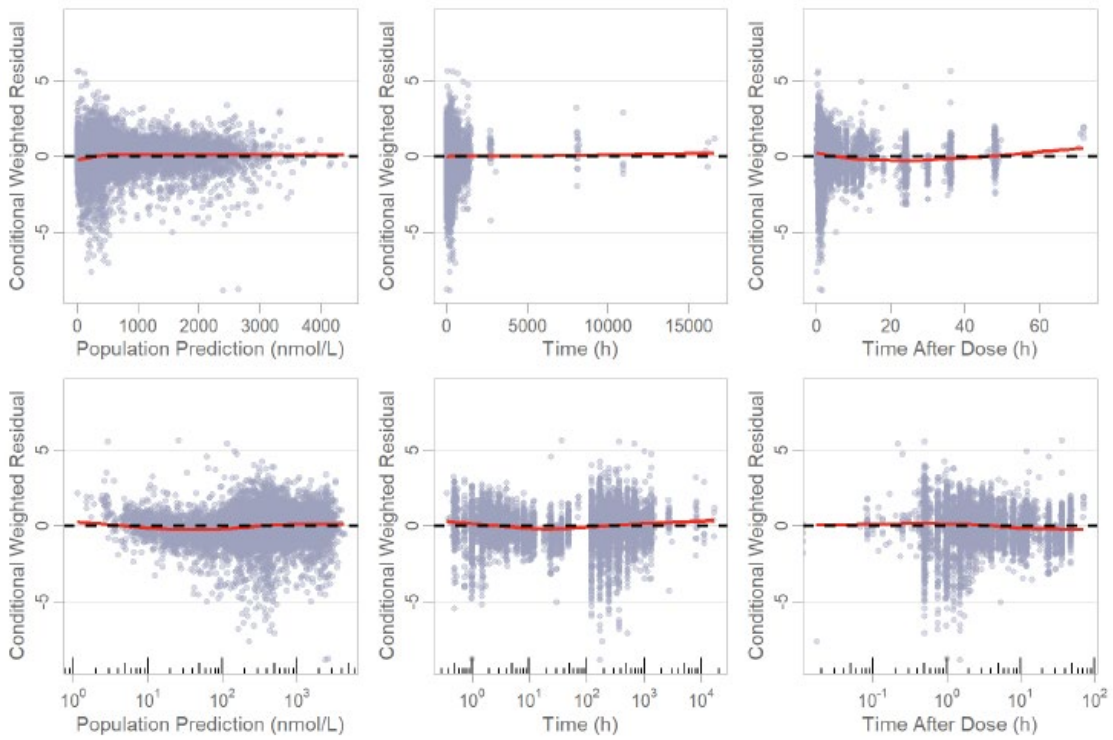
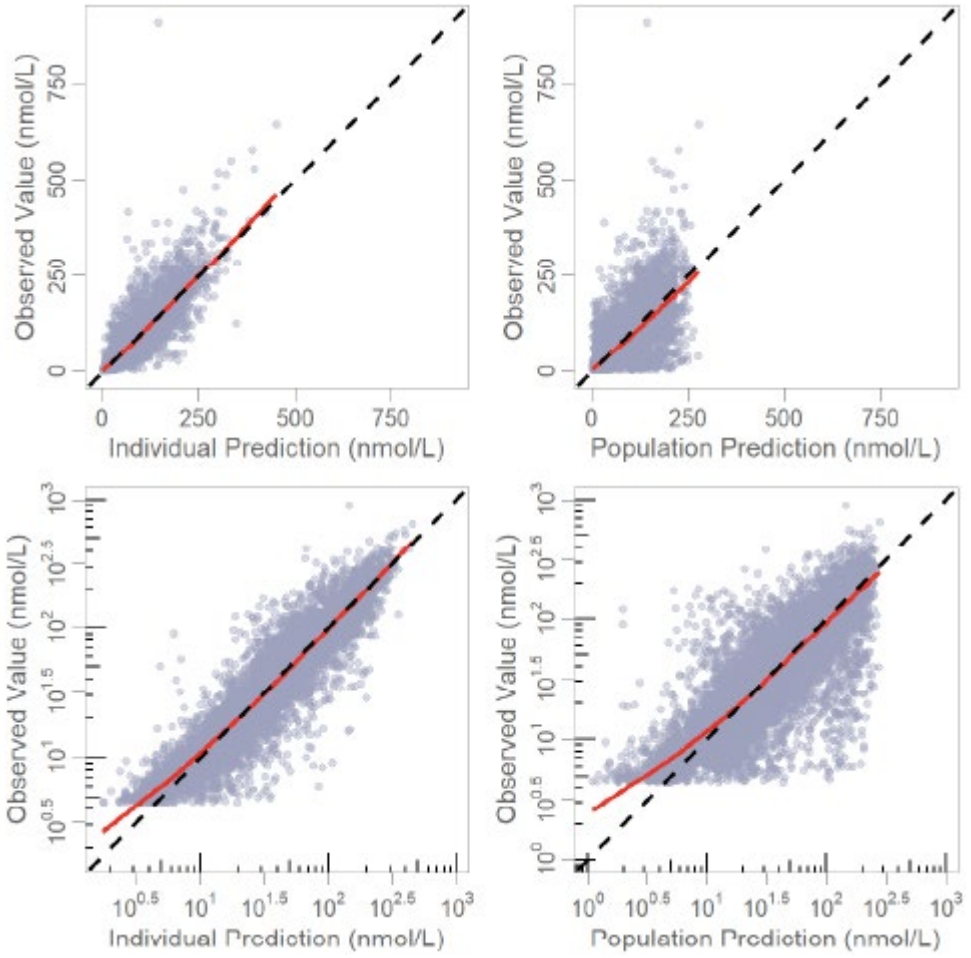


Figure 9. Final Population PK Model of N-Desmethyl Selumetinib: Goodness-of-Fit.



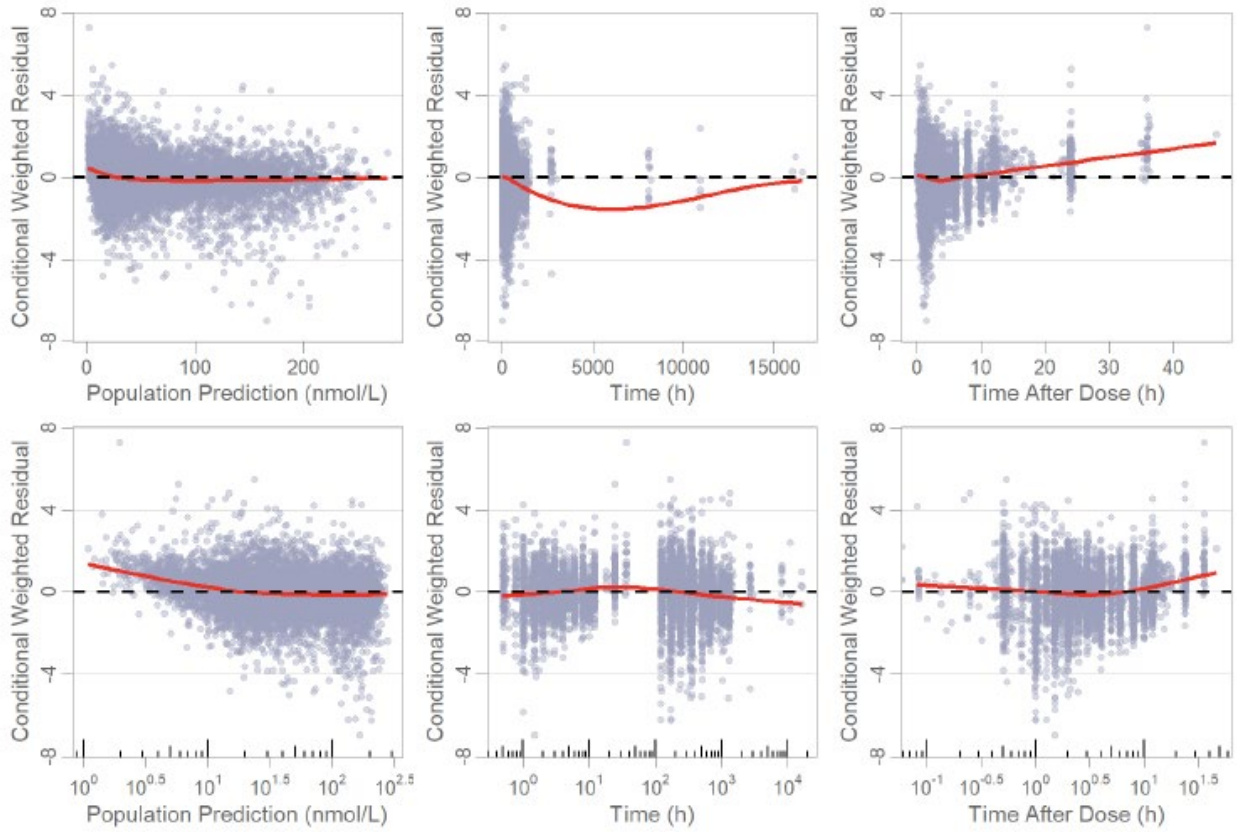


Figure 10. Final Population PK Model – Selumetinib - Goodness-of-Fit – Study D1346C00004 (SPRINKLE)

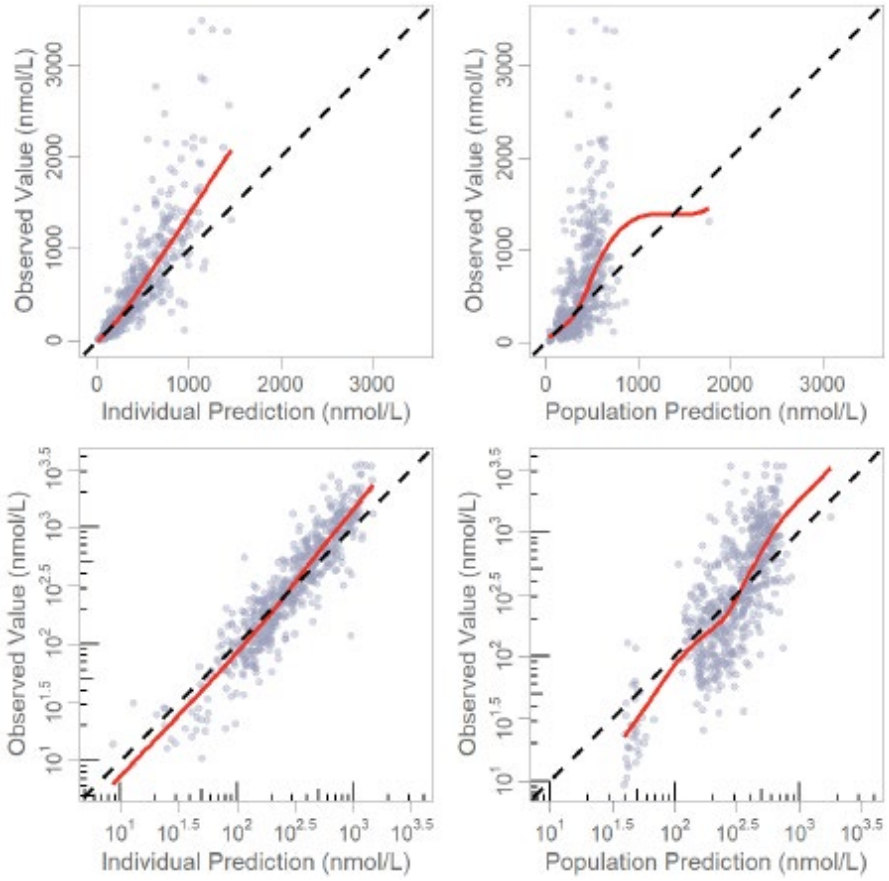


Figure 11. Final Population PK Model –Selumetinib - Goodness-of-Fit – Age Group ≥1 to < 3 years

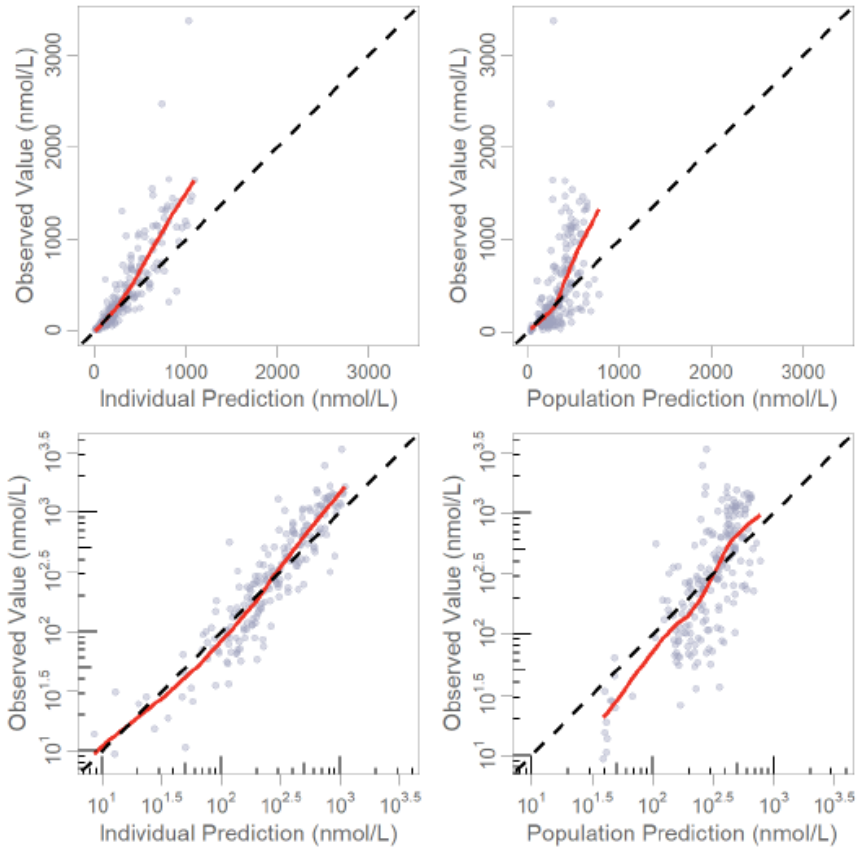


Figure 12. Final Population PK Model –Selumetinib - Goodness-of-Fit – Age Group ≥3 to < 7 years

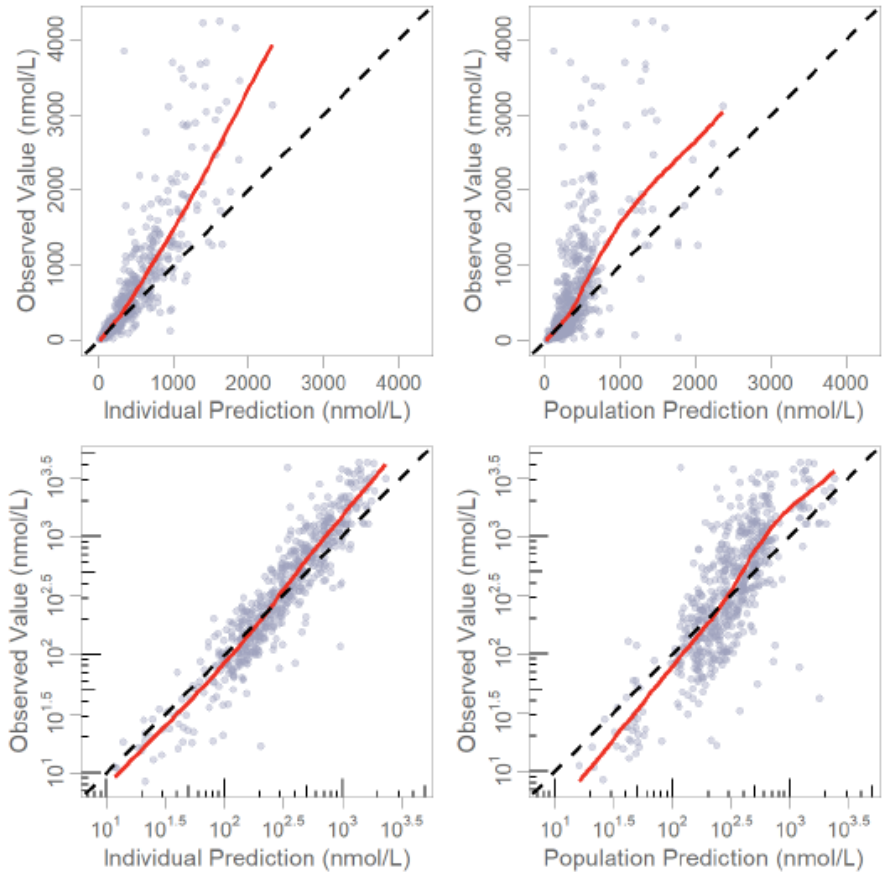


Figure 13. Prediction-Corrected Visual Predictive Check of Selumetinib Concentrations Overlaid with Observations - Semi-Log Scale

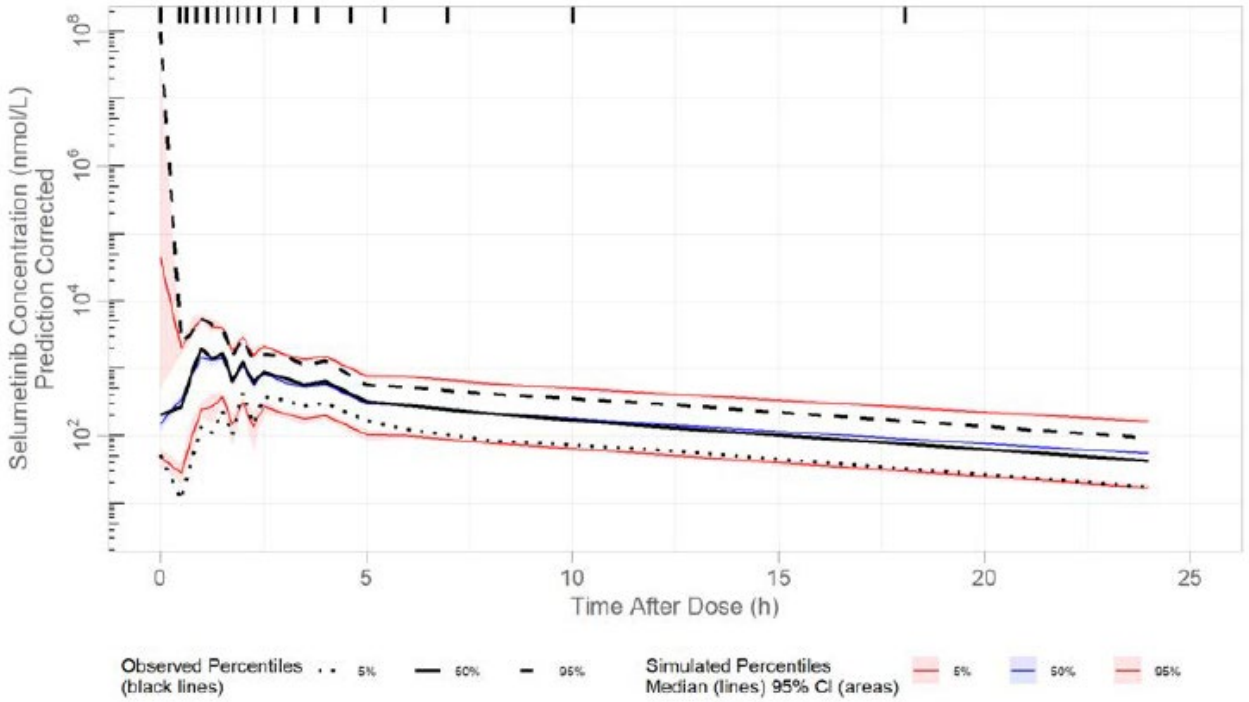


Figure 14. Prediction-Corrected Visual Predictive Check of N-demethyl Selumetinib Concentrations Overlaid with Observations - Semi-Log Scale

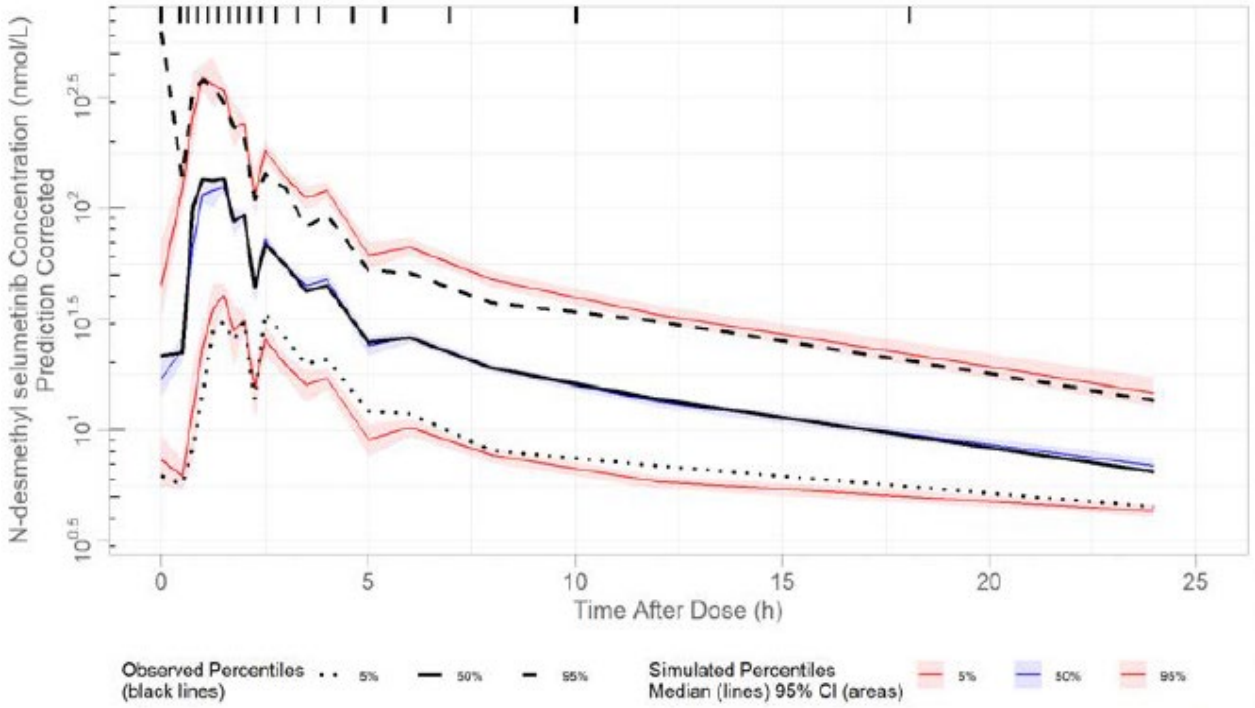


Figure 15. Final Population PK Model – Selumetinib - Prediction-Corrected VPC – By Formulation – Semi-Log Scale

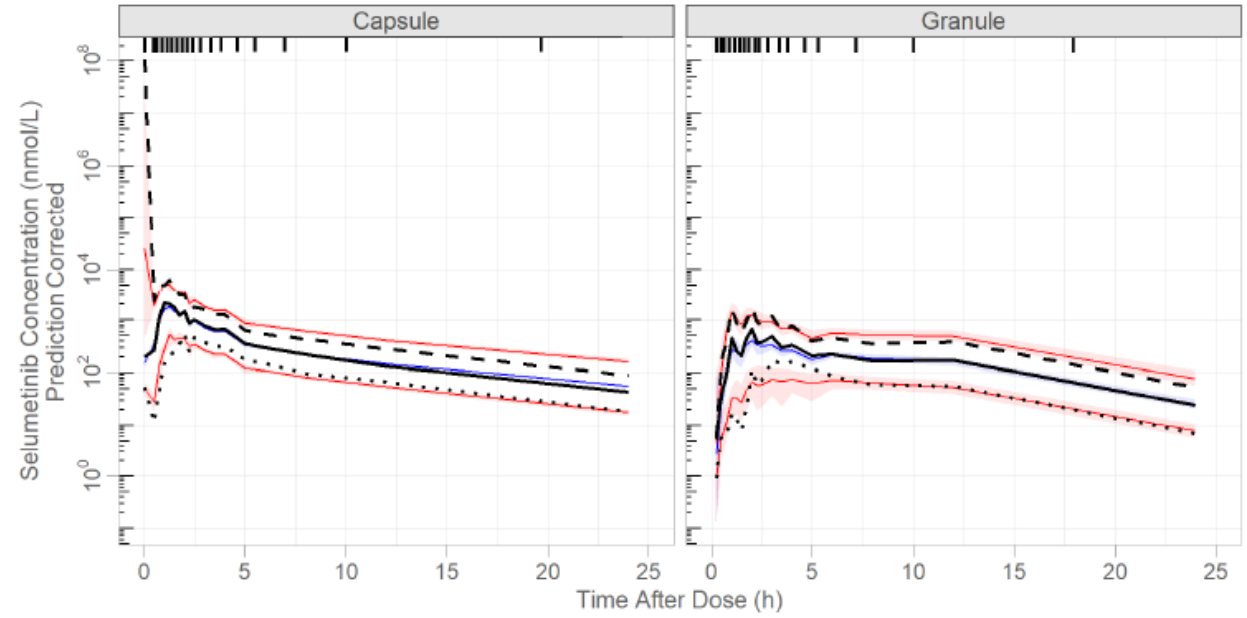
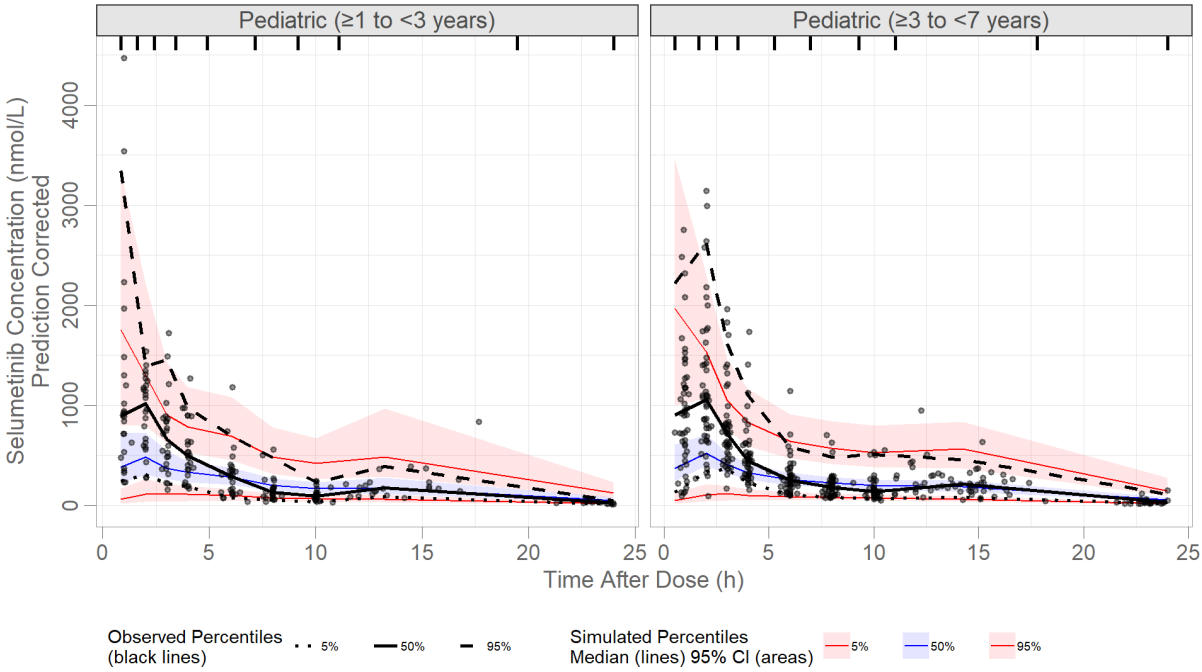
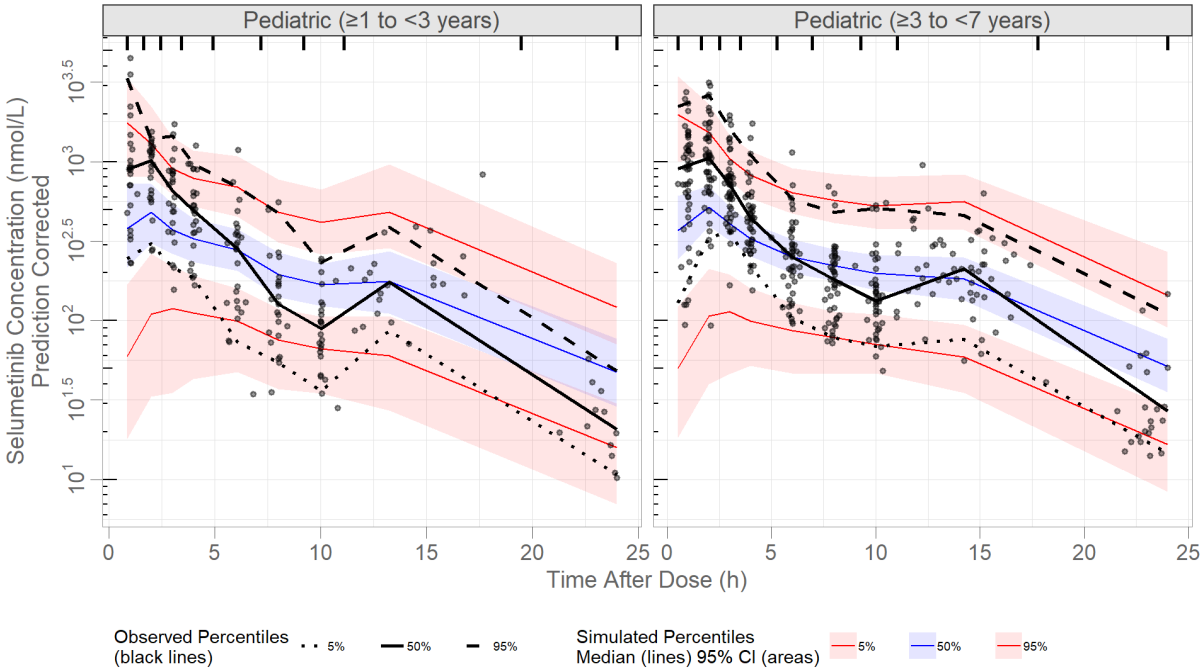


Figure 16. PcVPC of Selumetinib in the Sprinkle Study (with Stratification by Age Groups (1 to < 3 and 3 to < 7 years)



Source: REDUCE_VPC_Sprinkle_by_AgeGroup.html



Source: REDUCE_VPC_Sprinkle_by_AgeGroup.html

Special populations

No new data with the granule formulation are provided / submitted in special populations, except PK data from 4 paediatric Japanese patients included in the SPRINKLE Study.

Pharmacokinetic interaction studies

No new information are provided.

2.6.2.2. Pharmacodynamics

Pharmacokinetics-Pharmacodynamics (PK/PD)

PK Modelling

No exposure-response for efficacy analysis was performed in paediatric patients with NF1 aged 1-<7 years old (SPRINKLE study) as no formal efficacy data were available / provided based on the cut-off date of 08 Apr 2024.

In the reference paediatric population NF1 aged 3 to 18 years old (SPRINT study), the relationship between steady state AUCss (as an exposure endpoint) and the probability of observing a response in terms of Objective response rate (ORR) as per the Independent Central Review (ICR) dataset, exposure-ORR relationship was marginally significant (p = 0.0428).

In PMX-0116.01, an analysis was performed to compare the observed AUC_{ss} values of selumetinib in Cycle 2 Day 1 dose in pediatric participants ≥ 1 to < 3 years, ≥ 3 to < 7 years, and ≥1 to < 7 years enrolled in SPRINKLE vs. PopPKpredicted- steady state AUC (AUC_{ss}) in the SPRINT Phase II Stratum 1 (referring to modelling report MS-01) in the ≥ 3 to < 7 years and ≥ 3 to ≤ 18 years. Descriptive statistics for selumetinib in PopPKpredicted- AUC_{ss} in SPRINT and the NCAderived- AUC_{ss} in Cycle 2 Day 1 in SPRINKLE by age group are presented in **Table 19**.

Table 19: PopPK-predicted Descriptive Statistics for the AUC_{ss} of Selumetinib in SPRINT and the NCA-derived AUC_{ss} in Cycle 2 Day 1 by Age Group in SPRINKLE (≥1 to < 3 Years, ≥ 3 to < 7 Years, and ≥ 1 to < 7 Years)

Study	Age Group	N Mean (CV) Geometric Mean (CV) Median [Min; Max] [5th Percentile; 95th Percentile]	
		AUC_{ss} (nM.hr)	AUC_{ss} (ng × h/mL)
SPRINKLE	≥ 1 to < 3 years	N = 11 4810 (46.2%) 4310 (54.3%) 4370 [1940; 8200] [2010; 7770]	N = 11 2200 (46.2%) 1970 (54.3%) 2000 [888; 3750] [922; 3560]
	≥ 3 to < 7 years	N = 22 6720 (50.9%) 6110 (44.8%) 6040 [3310; 18100] [3460; 11400]	N = 22 3080 (50.9%) 2800 (44.8%) 2770 [1510; 8290] [1580; 5210]
	≥ 1 to < 7 years	N = 33 6090 (52.1%) 5440 (50.7%) 5880 [1940; 18100] [2640; 11100]	N = 33 2790 (52.1%) 2490 (50.7%) 2690 [888; 8290] [1210; 5080]
SPRINT	≥ 3 to < 7 years	N = 18 5650 (29.5%) 5440 (27.8%) 5340 [3670; 10100] [3680; 8640]	N = 18 2580 (29.5%) 2490 (27.8%) 2450 [1680; 4630] [1680; 3960]
	≥ 3 to ≤ 18 years	N = 68 5180 (23.5%) 5060 (21.6%) 4950 [3440; 10100] [3680; 7180]	N = 68 2370 (23.5%) 2320 (21.6%) 2270 [1570; 4630] [1680; 3290]

AUCss within dose internal (12 hours) based on Cycle 2 Day 1 dose for SPRINKLE study and PopPK model-predicted values for SPRINT study.
Note: NCA-derived AUC_{ss} (Cycle 2 Day 1) are presented for SPRINKLE study and model-predicted AUC_{ss} from PopPK report (MS-01) are presented for SPRINT study.

Exposure-Response analysis for Safety

Exposure-response analysis of adverse events (AEs) of interest was performed in paediatric patients with NF1 aged 1-<7 years old (SPRINKLE study).

AEs were classified according to the CTCAE Grade system version 5.0, encompassing grades 0 (None), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Life-threatening), and 5 (Death). Frequency counts were derived by CTCAE grade for a range of AEs, including rash acneiform, rash non-acneiform, dermatitis and eczema, skin infection, nail disorders, oral mucositis, leukopenic events, lymphopenic events, neutropenic events, thrombocytopenic events, erythropenic events, cardiac toxicity, muscular toxicity, acute kidney injury, chromaturia, hypocalcemia, ocular toxicity, nausea, vomiting, diarrhoea, hepatotoxicity. In addition, TTO (time to onset) and adverse events actions (no change, dose changed, withdrawn) were also explored.

The primary analyses were performed using the steady state NCA-derived AUCss of selumetinib. Additional analyses using the model-based (modelling report PMX-0116.01) predicted exposure parameters (i.e., selumetinib, N-desmethyl selumetinib, total moiety and potency adjusted total

moiety) as well as predicted daily PK exposure parameters at the day of the observed AE (acAUC, AUCday, Cmax,day, and Cmin,day) were also performed.

The distribution of adverse events across tertiles of AUCss are presented in **Table 20**.

Table 20: Distribution of Adverse Events Across Tertiles of NCA-Derived AUC_{ss} of Selumetinib in SPRINKLE

Adverse Event	Frequency (%) of Events		
	1st Tertile of AUC_{ss} N=11 3432 [1941;4220]	2nd Tertile of AUC_{ss} N=11 5875 [4369;6279]	3rd Tertile of AUC_{ss} N=11 8197 [6807;18108]
Rash acneiform any grade	0 (0%)	0 (0%)	1 (9.09%)
Rash non-acneiform any grade	5 (45.5%)	2 (18.2%)	4 (36.4%)
Rash non-acneiform grade 2 or higher	1 (9.09%)	0 (0%)	1 (9.09%)
Dermatitis and Eczema any grade	3 (27.3%)	4 (36.4%)	5 (45.5%)
Dermatitis and Eczema grade 2 or higher	1 (9.09%)	2 (18.2%)	1 (9.09%)
Skin infection any grade	4 (36.4%)	2 (18.2%)	3 (27.3%)
Skin infection grade 2 or higher	2 (18.2%)	2 (18.2%)	2 (18.2%)
Nail disorders any grade	2 (18.2%)	7 (63.6%)	6 (54.5%)
Nail disorders grade 2 or higher	0 (0%)	4 (36.4%)	6 (54.5%)
Nail disorders grade 3 or higher	0 (0%)	0 (0%)	1 (9.09%)
Ocular toxicity any grade	1 (9.09%)	0 (0%)	1 (9.09%)
Oral mucositis any grade	1 (9.09%)	4 (36.4%)	1 (9.09%)
Oral mucositis grade 2 or higher	0 (0%)	1 (9.09%)	0 (0%)
Neutropenic events any grade	0 (0%)	1 (9.09%)	0 (0%)
Thrombocytopenic events any grade	1 (9.09%)	0 (0%)	0 (0%)
Erythropenic events any grade	3 (27.3%)	2 (18.2%)	2 (18.2%)
Erythropenic events grade 2 or higher	1 (9.09%)	2 (18.2%)	1 (9.09%)
Cardiac toxicity any grade	1 (9.09%)	0 (0%)	0 (0%)
Muscular toxicity any grade	3 (27.3%)	3 (27.3%)	4 (36.4%)
Muscular toxicity grade 2 or higher	1 (9.09%)	3 (27.3%)	1 (9.09%)
Muscular toxicity grade 3 or higher	1 (9.09%)	0 (0%)	0 (0%)
Nausea any grade	1 (9.09%)	0 (0%)	1 (9.09%)
Vomiting any grade	6 (54.5%)	5 (45.5%)	2 (18.2%)
Vomiting grade 2 or higher	0 (0%)	3 (27.3%)	0 (0%)
Diarrhea any grade	6 (54.5%)	4 (36.4%)	3 (27.3%)
Diarrhea grade 2 or higher	1 (9.09%)	2 (18.2%)	0 (0%)
Hepatotoxicity any grade	2 (18.2%)	0 (0%)	2 (18.2%)

Note: The mid-point (range) of the AUCss in the 1st, 2nd and 3rd tertiles were 3432 nM × h [1941 to 4220], 5875 nM × h [4369 to 6279] and 8197 nM × h [6807 to 18108], respectively.

A flat exposure-response relationships between selumetinib NCA-derived AUCss and rash acneiform, dermatitis events, dermatitis and eczema events, oral mucositis events, thrombocytopenic events erythropenic events, cardiac toxicity, hepatotoxicity events and ocular toxicity events.

Selumetinib exposure in the 3rd tertile reveal a slightly higher proportion of rash non-acneiform Grade 1 events, skin infection grade 2 events, and nail disorders events of grade 2 and 3 and selumetinib exposure in 2nd and 3rd tertile presented with a slightly higher proportion of muscular toxicity events of grade 2 and 3. However, no statistically significant relationship was observed based on the logistic regression analyses .

Overall, no clear relationship between systemic exposure on selumetinib and adverse events of interest were observed.

2.6.3. Discussion on clinical pharmacology

In the current application, a MA extension is submitted to register a new pharmaceutical formulation of selumetinib as granules in capsule for opening (two strengths 5 mg and 7.5 mg) and to extend the currently authorised indication (treatment of paediatric patients aged 3-18 years old with NF1 who have symptomatic, inoperable PN) to patients with NF1 aged 1-3 years old.

The granule formulation is intended to be used in patients 1-<7 years old and in older patients that have swallowing difficulties, the recommended dose is the same than that approved for the capsule formulation, 25 mg/m^2 BID dose based on BSA.

The clinical pharmacology of selumetinib granules is primarily based on a pivotal Phase 1/2 study D1346C0004 (SPRINKLE study) conducted in paediatric population aged 1 to <7 years with NF1 who received the granule formulation (rich PK data after the first dose and at steady state were available), and supported by PK data from the relative BA and food effect Phase 1 study 89 comparing the biopharmaceutical performances of the capsule and the granule formulations. Integrated Pop-PK analyses (reports PMX-0116.01 and PMX-0116.01.a) combining capsules and granules PK data were provided, along with an exposure-response analysis for safety events in the SPRINKLE study. Importantly, a request for extrapolation based on the matching systemic exposure (AUCss) approach of efficacy outcomes from paediatric patients 3-18 years old (Reference Sprint study) to the new target population 1-3 years was applied for.

Mechanism of action of selumetinib is known.

Bioanalysis

There are no new bioanalytical methods included in this submission. The HPLC-MS/MS method "ANAHPP" used to quantify plasma selumetinib and its active metabolite N-desmethyl selumetinib in SPRINKLE study have been previously submitted and considered adequate. Validation and in-study reports, including Incurred Sample Reanalysis (ISR) data, are provided with overall satisfactory results.

PKs of the granule formulation

At the recommended dosage of 25 mg/m2 BID in paediatric patients aged 1-7 years old, the geometric means (gCV%) of Cmax following the first dose and at steady state were 503 ng/mL (49%) and 657 (58%) ng/mL, respectively. The geometric means (gCV%) of AUC0-12h following the first dose and at steady state were 1790 (28%) ng.h/mL and 2575 (52%), respectively. The accumulation was 1.3-fold and 1.46-¬fold and for Cmax and AUC0-12h, respectively following administration of selumetinib granules 25 mg/m2 BID.

The median Tmax after single dose and at steady state of selumetinib granules was 2 to 2.5 hours post dose, indicating marginally slower absorption in comparison to the capsule formulation (Tmax of 1 to 1.5 hours. The geometric means (gCV%) of apparent oral clearance (CL/F), apparent volume of distribution (Vz/F) and terminal half-life were 7.1 L/h (gCV% = 34%), 75.3 L (44%) and 7.4 hours (gCV% =50%). Conversion to the N-desmethyl metabolite from parent was low with geometric mean metabolite to parent ratio of 7 to 8% after single dose and around 6% at steady state. As expected, the new proposed immediate release formulation showed a similar PK profile / properties (Tmax, Vd, CL, T1/2 half-live, accumulation) to that known for the capsule formulation.

The food effect model (Report PMX-0057.00, submitted with initial application) analysis also showed that concomitant administration of a low or high fat meal resulted in a mean decrease in the exposure (AUC) of selumetinib when compared to fasted administration which was not considered clinically relevant. Based on the above results, the effect of food (high-fat, low-fat and without regard to food) for both formulations (capsules and granules) is not expected to result in a clinically relevant impact on the AUC of selumetinib since the magnitude of effect on the oral administration bioavailability (F1) is less than 30%.

Comparison of biopharmaceutical performances of granule and capsule formulations

In the relative bioavailability Phase 1 study 89 (n= 24 healthy volunteers, cross over design), selumetinib dose-normalized AUC/D decreased slightly by 13.5% and Cmax/D decreased by 35% following administration of the granule formulation (25 mg) in comparison to capsules (50mg) at the fasted state, with geometric mean ratios (90%CI) of 0.865 (0.811, 0.922) and 0.654 (0.581, 0.736) for AUC and Cmax, respectively.

In Sprinkle study in patients 1-<7 years old, the granule formulation, administered at 25 mg/m2, achieves 11% lower AUC0-12h after single dose (geometric mean AUC-012h = 1790 ng.h/mL) to that observed with the capsule formulation (AUC0-12h = 2009 ng/mL) used in the reference SPRINT Phase 2 study (patients 3-18 years old). the exposure comparability is supported by the finding that the 90% CI of the geometric mean granule AUC0-12 for both cohort 1 and 2 were within the [80% -125%] limits of the mean AUC0-12 of SPRINT study, except the lower bound of the 90% CI for the global cohort 2 that was 74% (just below the 80% limit). However, it is noted that granule Cmax is decreased by approximately 31% relative to capsules (503 ng/mL versus 731 ng/mL in SPRINT).

Overall, consistent findings are drawn in healthy volunteers and in patients, indicating that the granule formulation achieves comparable systemic exposure AUC levels but 30% to 35% lower Cmax compared to the capsule formulation. Given that AUC, rather than Cmax, is the key PK parameter driving clinical efficacy for selumetinib, it is agreed that the granule formulation designed to facilitate dosing in paediatric patients does not negatively impact in vivo performance.

Pop-PK analysis (Report PMX-0116.01)

An updated Pop-PK analysis was performed by integrating the new PK data from 3 clinical studies, including in particular those from SPRINKLE study (n = 36; n = 32 in the global cohort and n = 4 in the Japan cohort), to the previous PK dataset collected from 15 studies. The final population dataset included 10412 plasma selumetinib, 217 radioactive C14 compound and 8601 plasma N-desmethyl selumetinib concentrations available from 591 subjects across 18 studies. As expected, similar to the original food effect model (Report PMX-0057.00), the PKs of selumetinib was well described by a two-compartment model with sequential zero- and first-order delayed absorption and first-order elimination and one-compartment model for the N-desmethyl metabolite. In addition, to the already identified covariate effects, the effect of formulation (capsule vs granule) and healthy status on Ka, the effect of drug administration without regard to food on F1 and D1 and the effect of baseline Albumin on Fm were retained in the final model.

In general, parameter estimates were consistent with those derived in the original Pop-PK analysis, with the exception of Ka (5.71 h-1 versus 7.14 h-1 previously). Overall, all population PK parameters were precisely estimated (RSE <20%), except for F1 (21.5%), the effect of age on CL and meal covariate on D1 (RSE of 28.9% and 36.5%). The shrinkages of individual random effects were <30%, no major bias was observed in the GOF plots for the overall data of selumetinib and N-desmethyl selumetinib and the provided pcVPC show an overall good agreement between observed and model-based predicted data.

However, the standard goodness-of-fit plots (DV vs PRED and DV vs IPRED) from the SPRINKLE study, including by age groups [1–3] and [3–7] years, showed a clear bias toward under-prediction of higher concentrations. Due to the reliance on observed (NCA-derived) PK data in the submission, it is concluded that the current Pop-PK model is not adequate for the SPRINKLE population and cannot be used to support dosing recommendations or efficacy extrapolation in young children.

Effect of BSA / age on selumetinib exposure

A ~30% lower geometric mean AUCss was observed in patients aged 1–<3 years compared to those aged 3–<7 years in the SPRINKLE study (1970 vs. 2800 ng·h/mL), suggesting possible underexposure in younger children and those with lower BSA. Boxplots and summary statistics confirmed lower AUCss in the younger age group, with the lowest values seen in the 0.40–0.49 m² BSA subgroup. However, as this finding is based on a single patient (n=1), no robust conclusion was drawn regarding the extent or clinical relevance of underexposure in this subgroup.

Extrapolation of efficacy in patients aged 1–<3 years

No formal efficacy data were available from SPRINKLE study (actual report submitted with DCO of 08 Apr 2024).

A paediatric efficacy extrapolation strategy was applied, based on matching exposure between the reference population (children with NF1 aged 3–18 years, SPRINT study) and the target population (children aged 1–<3 years, within SPRINKLE study). In children 1–<3 years, geometric mean AUCss was 2028 ng·h/mL, on average 27% lower than in patients aged 3–<7 years in SPRINT (2791 ng·h/mL; GMR = 0.73, 90% CI 0.54–0.98; 95% CI 0.51–1.04), and 13% lower than in the overall 3-18 years population (2334 ng· h/mL; GMR = 0.87, 90% CI 0.74-1.02; 95% CI 0.71-1.06). The defined effective exposure range in SPRINT was 1585-4632 ng· h/mL. In SPRINKLE, the lower bound of the 90% CI was 1493 ng· h/mL (≈6% below the efficacy threshold) and the 95% CI 1390 ng· h/mL (≈13% below). This corresponds to a low probability (≈2.5-5%) of falling below the efficacious range. Given the flat exposure-response relationship observed in SPRINT, the risk of underexposure is considered limited, supporting adequate coverage in the target population.

To address potential risk of underexposure in the lowest BSA subgroup, the MAH proposed a 25% dose increase for patients with BSA 0.40-0.49 m² (10 mg → 12.5 mg BID). This adjustment is expected to bring selumetinib and metabolite (N-desmethyl selumetinib) exposures closer to those observed in SPRINT, compensating for both formulation- and age-related differences.

No correlation between Cmax and efficacy was observed in SPRINT despite emerging data from a parallel variation procedure . From a practical standpoint, the proposed 25% posology increase is expected to proportionally increase both AUCss and Cmaxss, addressing potential shortfalls. Consequently, AUCss remains the most relevant and robust exposure metric for extrapolation. On this basis, the principle of extrapolation to children 1–<3 years is considered agreeable.

The currently tested dose of 20 mg BID in SPRINKLE remains the standard and provides the only clinically validated safety and exposure data. For patients who can tolerate dose escalation, an increase to 25 mg BID may be considered on an individual basis, taking into account clinical response

and safety. This approach allows the extrapolation principle to be implemented while minimizing risk, and also enables the collection of additional PK and safety data at the higher dose for future refinement of the posology recommendations.

2.6.4. Conclusions on clinical pharmacology

The PK of the new proposed granule formulation of selumetinib had been sufficiently characterised and achieved overall comparable systemic exposure levels to those observed with the approved capsule formulation. Thus, the addition of the granules is considered acceptable from a PK perspective.

The extrapolation of efficacy to patients aged 1–<3 years is agreed on. In SPRINKLE, geometric mean AUCss in children 1–<3 years was 2028 ng·h/mL, on average 13% lower than in the overall 3–18 years population (2334 ng·h/mL), with a flat exposure–response relationship observed in SPRINT. To mitigate the potential risk of underexposure in the lowest BSA subgroup, a stepwise 25% dose increase was recommended on an individual basis, taking into account clinical response and safety.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

See main study.

2.6.5.2. Main study

Title

A Phase I/II, Single-Arm, Open-label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE)

Methods

The SPRINKLE study is a Phase I/II, single arm, open-label study in children aged ≥ 1 to< 7 years at study entry with a clinical diagnosis of NF1 with symptomatic, inoperable PN. The study was designed to define the dose regimen and evaluate the PK, safety, and tolerability of selumetinib given as a granule formulation.

The study included an initial dose-finding period to identify and confirm an acceptable dose schema for the granule formulation of selumetinib followed by a 25-week treatment period and a safety follow-up period for up to 5 years.

Intervention phase

The intervention phase included an initial dose-finding period designed to identify an acceptable dose schema for the selumetinib granule formulation. Dosing commenced in Global Cohort 1 during the dose-finding period according to the proposed dose schema equivalent to 25 mg/m² bid. An SRC review of safety and PK data was performed after 3 evaluable participants in Cohort 1 had completed 1 cycle (28 days) of treatment to determine whether the proposed granules formulation dose was safe

and produced exposure within the targeted, acceptable range identified in the SPRINT Phase II Stratum I study (*Figure 17*).

Figure 17: Dose-Finding Process Schematic

All participants were required to complete at least 3 cycles of treatment with the granule formulation. Participants who attain a BSA between 1.10 and 1.29 m² and complete at least 3 cycles of treatment with the granule formulation were encouraged to transition to the capsule formulation.

All participants receive continuous selumetinib bid for 25 cycles (or until they meet discontinuation criteria). Participants who are younger than 5 years of age after 25 cycles of selumetinib entered a safety follow-up phase until they reach the age of 5 years or commence an alternative systemic NF1-PN treatment, whichever is earliest.

Safety follow-up phase

Long-term safety follow-up was also to be performed for participants who were < 3 years of age when they commenced selumetinib until they were ≥ 5 years of age or commence an alternative systemic

NF1-PN targeted treatment, whichever was earlier. Participants could continue to receive selumetinib (capsule or granule formulations) during the long-term safety follow-up phase as long as the Investigator considered they were receiving benefit.

Study Participants

Key inclusion criteria included:

- Male and female participants (≥ 1 to < 7 years of age with BSA ≥ 0.4 and ≤ 1.09 m2 at enrollment)
- With a diagnosis of NF1 who have symptomatic, inoperable PN.
- Participants were also required to have PN measurable by volumetric MRI analysis and Lansky performance of ≥ 70, except for participants who were wheelchair-bound.

Key exclusion criteria included:

- confirmed or suspected malignant glioma or malignant peripheral nerve sheath tumours;
- refractory nausea and vomiting, chronic gastrointestinal disease,
- inability to swallow the formulated product.

Three participant cohorts were enrolled:

Global Cohort 1: participants enrolled outside Japan aged between ≥ 4 and < 7 years,

Global Cohort 2: participants enrolled outside Japan aged between ≥ 1 and < 4 years,

Japan Cohort: Japanese participants in Japan aged between ≥ 1 and < 7 years.

Treatments

Selumetinib granules were administered bid, approximately 12 hours apart. Granules from the sprinkle capsule were to be dispensed on or mixed with a suitable food vehicle such as smooth flavoured or natural yogurt, smooth fruit sauce, smooth fruit puree, or smooth fruit jam prior to ingestion.

Participants ≥ 1 to < 4 years of age could take selumetinib granules without regard to food on all study days.

Participants aged ≥ 4 to < 7 years were instructed to take selumetinib granules fasted on intensive PK sampling days (Day 1 of Cycles 1 and 2) and without regard to food on other study treatment days.

When applicable, selumetinib capsules were to be administered on an empty stomach.

Table 21 Investigational Products

Intervention name	Selumetinib	Selumetinib
Type	Drug	Drug
Dose formulation	Granule	Capsule
Unit dose strength(s)	5 mg and 7.5 mg granule formulation in sprinkle capsules	10 mg and 25 mg capsules
Dosage level(s)	Dose finding starting with equivalent to 25 mg/m^2 bid (12 hours apart)	25 mg/m^2 bid (12 hours apart)
Route of administration	Oral	Oral
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labelling	Study intervention was supplied as 5 mg (white/white) and 7.5 mg (white/blue) sprinkle capsules in 60 count bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Labels were prepared in accordance with GCP Ordinance.	Study intervention was supplied as 10 mg (white) and 25 mg (blue) capsules in 60 count bottles. Each bottle was labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Labels were prepared in accordance with GCP Ordinance.
[Current/former name(s) or alias(es)]	AZD6244 KOSELUGO®	AZD6244 KOSELUGO®

Table 22 Proposed Selumetinib Granule Formulation Dose Schema

BSA (m^2)	**Granules Dose (bid approximately 12 hours apart)**	**Dose level (mg/m^2)**
0.40 - 0.49	10 mg	20.4 – 25.0
0.50 - 0.59	12.5 mg	21.2 – 25.0
0.60 - 0.69	15 mg	21.7 – 25.0
0.70 - 0.89	20 mg	22.5 - 28.9
0.90 - 1.09	25 mg	22.9 - 27.8
1.10 - 1.29 [a]	30 mg	23.3 - 27.3

a In the rare circumstance that a participant is unable to transition to capsule selumetinib when they attain a BSA between 1.1.0 and 1.29 m^2 participants can continue to receive the granule formulation.

Only 1 dose of selumetinib was taken on Day 1 of Cycle 1 ; bid dosing started on Day 2 of Cycle 1.

Objectives / Outcomes/endpoints

The study endpoints evaluated in this CSR (DCO1) after all participants (Global and Japan Cohorts) had the opportunity to complete 3 cycles of treatment are presented in a single table.

Table 23. Primary Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the PK of selumetinib after administration of the selumetinib granule formulation.	• Selumetinib AUC0-12 derived after single dose administration.
• To assess the safety and tolerability of the selumetinib granule formulation.	• Safety and tolerability will be evaluated in terms of AEs, clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis), physical examination, weight, vital signs, ECG, ECHO, ophthalmologic assessment, knee (or wrist) MRI/X-ray, and performance status. • Assessments related to AEs will include: occurrence/frequency; relationship to study intervention; CTCAE grade; seriousness; death; AEs leading to discontinuation of study intervention; AEs of special interest.
Secondary	
• To assess the palatability of the selumetinib granule formulation	• Palatability will be assessed using the parent-reported observer palatability assessment.
• To further assess the PK of selumetinib and N-desmethyl selumetinib metabolite after administration of the selumetinib granule formulation.	• Plasma concentrations and PK parameters of selumetinib including, but not limited to: ° Selumetinib AUC0-12 derived after multiple dose administration. ° Cmax, AUC0-6, AUClast, CL/F, tmax, tlast derived after single and multiple dose administration. ° AUC0-24, Vz/F and t½λz after single dose administration. ° Rac Cmax, Rac AUC0-12, and Vss/F derived after multiple dose administration. • Plasma concentrations and PK parameters of N-desmethyl selumetinib including, but not limited to: ° Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after single and multiple dose administration. ° Rac Cmax and Rac AUC0-12 derived after multiple dose administration. • Parent-to-metabolite ratio for AUC0-6, AUC0-12 and AUC0-24 (single dose only), and Cmax after single and multiple dose administration.
• To evaluate the efficacy of the selumetinib granule formulation by assessment of ORR as determined by ICR per REiNS criteria.	• Objective Response Rate

Sample size

Sample sizes of 10, 15 and 20 in each Global Cohort were estimated to provide 90%, 99.9%, and 99.9% power, respectively, to demonstrate that the 95% CI of the AUC0-12 geometric mean of the

granule formulation of each cohort was within the 0.6 to 1.4-fold acceptance range of the geometric mean AUC0-12 observed in the SPRINT Phase II Stratum 1 study (2009 h*ng/mL). This sample size calculation assumed a ± 5% difference in exposure between the granule and capsule formulation and an inter-subject gCV% of 30%. The choice of gCV% was based on observations from Study 89 (27%) and the SPRINT Phase II Stratum I study (35%).

Approximately 38 participants were planned to be dosed in Cohorts 1 and 2 to achieve at least 30 evaluable participants, with at least 10 evaluable participants ≥ 1 to < 4 years of age (with at least 3 participants < 2 years of age) and at least 10 evaluable participants ≥ 4 to < 7 years of age at the recommended granule formulation dose schema for each cohort. The minimum sample size of each cohort was re-evaluated using the observed inter-subject gCV% after approximately 10 participants in Cohorts 1 and 2 had completed Cycle 1 at the final recommended dose. This review confirmed that 10 participants per cohort was sufficient to provide reasonable precision to characterize PK and safety.

The Japan Cohort was not included in the sample size calculations. At least 6 participants were planned for the Japan Cohort; however, due to recruitment difficulties, enrolment was suspended after 4 participants had been enrolled. The decision to suspend enrolment after 4 participants was made in consultation with and endorsed by the Japan Health Authority (PMDA).

Randomisation and blinding (masking)

Not applicable.

Results

Participant flow

Table 24. Disposition (Enrolled Participants)

	Global Cohort 1 (≥ 4 to < 7 years) N = 15 n (%)	Global Cohort 2 (≥ 1 to < 4 years) N = 17 n (%)	Total in Global N = 32 n (%)	Japan Cohort (≥ 1 to < 7 years) N = 4 n (%)	Total in study N = 39 n (%)
Participants enrolled	-	-	-	-	39
Screen failures	-	-	-	-	3
Participants started treatment	15 (100)	17 (100)	32 (100)	4 (100)	36 (100)
Participants completed treatment	1 (6.7)	0	1 (3.1)	0	1 (2.8)
Participants discontinued treatment	0	0	0	0	0
Participants who transitioned to capsule formulation	2 (13.3)	0	2 (6.3)	0	2 (5.6)
Participants ongoing on treatment at data cutoff date	14 (93.3)	17 (100)	31 (96.9)	4 (100)	35 (97.2)
Participants ongoing in study at data cutoff date	14 (93.3)	17 (100)	31 (96.9)	4 (100)	35 (97.2)
Participants completed study	1 (6.7)	0	1 (3.1)	0	1 (2.8)
Participants who entered the long-term safety follow-up [a]	0	0	0	0	0
Participants who discontinued treatment due to global/country situation (COVID-19 pandemic)	0	0	0	0	0
Participants who withdrew from study due to global/country situation (COVID-19 pandemic)	0	0	0	0	0

[a] Participants < 5 years of age after 25 cycles or discontinuation of study treatment.
Enrolled participants are those who signed informed consent.

Recruitment

First participant enrolled: 21 Jan 2022 Data cut-off: 08 Apr 2024

Conduct of the study

Table 25. Summary of Key Global Protocol Changes

Global amendment number	Summary of key changes in the amendment	Reason for amendment
Amendment 4.0 (Version 5.0) 15 Mar 2024	Non-substantial amendments to implement specific wording for new EU regulation and update section numbering.	To align protocol with EU specifications and correct typographical errors.
Amendment 3.0 (Version 4.0) 14 Feb 2023	Non-substantial amendment to clarify the requirement for data evaluation by SRC during the dose-finding phase after the first cycle of dosing to specify a maximum of 4 evaluable participants instead of the first 3 evaluable participants.	To ensure a minimum of 3 evaluable participants for dose-finding phase assuming screening failure rate and non-evaluable participants because of important PDs.
Amendment 2.0 (Version 3.0) 30 Nov 2022	Non-substantial amendment to add a new exploratory endpoint of potential biomarkers in residual PK or PD samples.	To facilitate biomarker analysis of residual PK or PD samples.
	Addition of adjustment criteria for the dose schema in the dose-finding phase.	To clarify that a difference <30% between the geometric mean AUC_{0-12} of SPRINKLE and SPRINT Phase II Stratum I studies would not require a dose adjustment.
Amendment 1.0 (Version 2.0) 18 Mar 2022	Added cohort of participants enrolled in Japan.	To generate PK and safety data from Japanese patients enrolled in Japan.
	• Added intensive PK sampling after transition of participants from granule to capsule formulation.	• Healthy Authority request.
	• Changed all references to QTcB to QTcF and references to corrected QT to QTcF. Clarified that QTcB and QTcF are to be collected at all timepoints throughout the study for participants enrolled prior to the amendment using QTcB at screening.	• Health Authority request.

Baseline data

Table 26. Demographics and Baseline Characteristics (Safety Analysis Set)

	Statistic	Global Cohort 1 (≥ 4 to < 7 years) N = 15	Global Cohort 2 (≥ 1 to < 4 years) N = 17	Total in Global N = 32	Japan Cohort (≥ 1 to < 7 years) N = 4	Total in study N = 36
Age (years)	Mean	5.08	2.49	3.70	4.43	3.78
	SD	1.101	0.819	1.619		1.681
	Median	4.40	2.50	3.70		3.90
	Min					
	Max					
Sex						
Female	n (%)	5 (33.3)	7 (41.2)	12 (37.5)	2 (50.0)	14 (38.9)
Male	n (%)	10 (66.7)	10 (58.8)	20 (62.5)	2 (50.0)	22 (61.1)
Race						
Asian	n (%)	1 (6.7)	0	1 (3.1)	4 (100)	5 (13.9)
Black or African American	n (%)	0	1 (5.9)	1 (3.1)	0	1 (2.8)
White	n (%)	9 (60.0)	13 (76.5)	22 (68.8)	0	22 (61.1)
Other	n (%)	2 (13.3)	2 (11.8)	4 (12.5)	0	4 (11.1)
Not reported	n (%)	3 (20.0)	1 (5.9)	4 (12.5)	0	4 (11.1)
Ethnicity						
Hispanic or Latino	n (%)	2 (13.3)	2 (11.8)	4 (12.5)	0	4 (11.1)
Not Hispanic or Latino	n (%)	13 (86.7)	15 (88.2)	28 (87.5)	4 (100)	32 (88.9)
Country						
Germany	n (%)	5 (33.3)	4 (23.5)	9 (28.1)	0	9 (25.0)
Italy	n (%)	3 (20.0)	6 (35.3)	9 (28.1)	0	9 (25.0)
Japan	n (%)	0	0	0	4 (100)	4 (11.1)
Russian Federation (the)	n (%)	2 (13.3)	0	2 (6.3)	0	2 (5.6)
Spain	n (%)	4 (26.7)	4 (23.5)	8 (25.0)	0	8 (22.2)
United States of America (the)	n (%)	1 (6.7)	3 (17.6)	4 (12.5)	0	4 (11.1)
BSA (m^2)	Mean	0.771	0.558	0.658	0.605	0.652
	SD	0.1073	0.0603	0.1369		0.1349
	Median	0.770	0.540	0.635		0.640
	Min					
	Max					
≥ 0.40 to < 0.50	n (%)	0	1 (5.9)	1 (3.1)	1 (25.0)	2 (5.6)
≥ 0.50 to < 0.60	n (%)	0	11 (64.7)	11 (34.4)	0	11 (30.6)
≥ 0.60 to < 0.70	n (%)	3 (20.0)	5 (29.4)	8 (25.0)	3 (75.0)	11 (30.6)
≥ 0.70 to < 0.90	n (%)	10 (66.7)	0	10 (31.3)	0	10 (27.8)
≥ 0.90 to < 1.10	n (%)	2 (13.3)	0	2 (6.3)	0	2 (5.6)
≥ 1.10 to ≤ 1.29	n (%)	0	0	0	0	0

Personal data removed from table

Baseline Disease Characteristics

Table 27. Baseline Disease Characteristics (Safety Analysis Set)

	Statistic	Global Cohort 1 (≥ 4 to < 7 years) N = 15	Global Cohort 2 (≥ 1 to < 4 years) N = 17	Total in Global N = 32	Japan Cohort (≥ 1 to < 7 years) N = 4	Total in study N = 36
Target PN symptoms*						
Any symptoms	n (%)	15 (100)	17 (100)	32 (100)	4 (100)	36 (100)
Vision loss	n (%)	2 (13.3)	1 (5.9)	3 (9.4)	1 (25.0)	4 (11.1)
Auditory loss	n (%)	2 (13.3)	0	2 (6.3)	0	2 (5.6)
Difficulty swallowing	n (%)	1 (6.7)	1 (5.9)	2 (6.3)	0	2 (5.6)
Abnormal speech	n (%)	0	1 (5.9)	1 (3.1)	0	1 (2.8)
Airway obstruction	n (%)	2 (13.3)	6 (35.3)	8 (25.0)	0	8 (22.2)
Respiratory compromise	n (%)	1 (6.7)	1 (5.9)	2 (6.3)	0	2 (5.6)
Bladder dysfunction	n (%)	0	1 (5.9)	1 (3.1)	0	1 (2.8)
Motor weakness	n (%)	1 (6.7)	1 (5.9)	2 (6.3)	1 (25.0)	3 (8.3)
Decreased range of motion	n (%)	2 (13.3)	2 (11.8)	4 (12.5)	1 (25.0)	5 (13.9)
PN-related disfigurement	n (%)	11 (73.3)	10 (58.8)	21 (65.6)	4 (100)	25 (69.4)
Pain	n (%)	6 (40.0)	8 (47.1)	14 (43.8)	2 (50.0)	16 (44.4)
Other symptom	n (%)	2 (13.3)	1 (5.9)	3 (9.4)	0	3 (8.3)
Overall target PN morbidity type *						
Airway	n (%)	3 (20.0)	6 (35.3)	9 (28.1)	0	9 (25.0)
Bowel/bladder	n (%)	0	1 (5.9)	1 (3.1)	0	1 (2.8)
Disfigurement	n (%)	12 (80.0)	10 (58.8)	22 (68.8)	4 (100)	26 (72.2)
Motor	n (%)	4 (26.7)	3 (17.6)	7 (21.9)	1 (25.0)	8 (22.2)
Pain	n (%)	6 (40.0)	8 (47.1)	14 (43.8)	2 (50.0)	16 (44.4)
Vision	n (%)	2 (13.3)	1 (5.9)	3 (9.4)	1 (25.0)	4 (11.1)
Other	n (%)	1 (6.7)	2 (11.8)	3 (9.4)	0	3 (8.3)
Number of target PN morbidities	Mean	2.1	1.8	2.0	8.5	2.7
	SD	1.36	0.73	1.06	12.37	4.29
	Min	1	1	1	1	1
	Median	2.0	2.0	2.0	3.0	2.0
	Max	6	3	6	27	27
Lansky performance status at Baseline						
(100) Fully active, normal	n (%)	9 (60.0)	13 (76.5)	22 (68.8)	3 (75.0)	25 (69.4)
(90) Minor restrictions in physically strenuous activity	n (%)	2 (13.3)	1 (5.9)	3 (9.4)	0	3 (8.3)
(80) Active, but tires more quickly	n (%)	4 (26.7)	3 (17.6)	7 (21.9)	1 (25.0)	8 (22.2)
NF1 diagnostic criteria*						
Any cafe-au-lait macules	n (%)	15 (100)	17 (100)	32 (100)	4 (100)	36 (100)
Freckling in axillary or inguinal region	n (%)	10 (66.7)	7 (41.2)	17 (53.1)	3 (75.0)	20 (55.6)
Optic pathway glioma	n (%)	5 (33.3)	5 (29.4)	10 (31.3)	0	10 (27.8)
Two or more iris Lisch nodules or 2 or more choroidal abnormalities	n (%)	2 (13.3)	0	2 (6.3)	1 (25.0)	3 (8.3)
A distinctive osseous lesion	n (%)	2 (13.3)	1 (5.9)	3 (9.4)	0	3 (8.3)
A NF1 heterozygous pathogenic variant	n (%)	9 (60.0)	13 (76.5)	22 (68.8)	0	22 (61.1)
A parent with NF1	n (%)	5 (33.3)	5 (29.4)	10 (31.3)	1 (25.0)	11 (30.6)

Numbers analysed

Table 28. Populations for Analysis

Analysis set	Description	Analyses
Enrolled set	All participants who signed the ICF.	Disposition summaries
PK analysis set	All participants who received at least 1 dose selumetinib and who had at least 1 post dose quantifiable plasma concentration with no IPDs potentially affecting the PK analysis.	All PK analyses
Safety analysis set	All enrolled participants who received at least 1 dose of selumetinib.	Safety analyses

Outcomes and estimation

No clinical efficacy data were provided in the CSR.

Palatability assessment

Table 29. Summary of Palatability Assessment Responses, Total Responses (Safety Analysis Set)

	Global Cohort 1 ≥ 4 to < 7 years) N = 15	Global Cohort 2 (≥ 1 to < 4 years) N = 17	Total in Global N = 32	Japan Cohort (≥ 1 to < 7 years) N = 4	Total in study N = 36
Item 1: Did your child take their study medication this morning/evening?					
Expected responses, n	420	392	812	84	896
Yes, n (%)	373 (88.8)	358 (91.3)	731 (90.0)	80 (95.2)	811 (90.5)
No, n (%)	5 (1.2)	2 (0.5)	7 (0.9)	0	7 (0.8)
Item 2: Reason for missing the dose (No responses to Item 1)					
Expected responses, n	5	2	7	0	7
Study doctor/nurse told to skip the dose, n (%)	2 (40.0)	1 (50.0)	3 (42.9)	0	3 (42.9)
Forgot to give the dose, n (%)	1 (20.0)	0	1 (14.3)	0	1 (14.3)
Child did not want to take the dose, n (%)	2 (40.0)	0	2 (28.6)	0	2 (28.6)
Item 3: Willingness to swallow (Yes responses to Item 1)					
Expected responses, n	373	358	731	80	811
Swallowed without problem, n (%)	317 (85.0)	277 (77.4)	594 (81.3)	74 (92.5)	668 (82.4)
Some resistance but did swallow, n (%)	14 (3.8)	72 (20.1)	86 (11.8)	0	86 (10.6)
Spit out some/all medication, n (%)	8 (2.1)	6 (1.7)	14 (1.9)	0	14 (1.7)
Vomited up medication, n (%)	0	0	0	0	0

Note: Each participant is expected to complete 2 daily entries during Week 1 of Cycle 1 and Cycle 7 until treatment discontinuation or transition to capsules. Item 2 is expected only for participants responding “No” to Item 1. Item 3 is expected only for participants responding either “Yes” to Item 1 or “No” to Item 1 and “Other” to Item 2.
Total includes the sum of the items collected at the Cycle 1 Week 1 and Cycle 7 Week 1 timepoints.
Percentages are calculated over the total number of expected entries at a given timepoint.

- **Summary of main efficacy results**

No clinical efficacy data were provided.

2.6.5.3. Clinical studies in special populations

Not applicable.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Data from SPRINT Phase II Stratum 1 showed an overall response rate (ORR) = 68.0% (34/50 participants; 95% CI, 53.3 – 80.5) in paediatric patients aged 3 to 18 years with NF1 who have symptomatic, inoperable plexiform neurofibromas PN.

The ORR was similar across age groups in SPRINT Phase II Stratum 1 study .

Table 30. ORR by Age at Study Entry in SPRINT Phase I and Phase II Stratum 1

Age group (years)	N	Number (%) of participants with response [a]	95% CI [b]
⩾ 3 to < 7	20	17 (85.0)	62.1, 96.8
⩾ 7 to < 12	25	15 (60.0)	38.7, 78.9
⩾ 12 to < 16	22	12 (54.5)	32.2, 75.6
⩾ 16	7	5 (71.4)	29.0, 96.3

a SPRINT Phase II Stratum 1: Response required consecutive confirmation within 3 to 6 months after the criteria for first response were met. SPRINT Phase I: Response required confirmation at least 4 weeks after the criteria for first response were met. Partial response = a decrease in the volume of the target PN by 20% or more compared with baseline.
b The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
ORR is defined as the number (%) of participants who received at least one dose of selumetinib and have at least one complete response or confirmed partial response occurring prior to study treatment discontinuation.

2.6.6. Discussion on clinical efficacy

In the frame of this line extension in combination with a type II variation, the MAH proposed a new age appropriate formulation, granules in capsules for opening (herein referred to as granule formulation) and initially sought for an of indication to paediatric patients aged 1 to less than 7 years.

The sought indication for the granule formulation was:

Koselugo as monotherapy is indicated for the treatment of paediatric patients aged 1 year to less than 7 years with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN).

The MAH did not provide any new efficacy data as no data were available from the SPRINKLE study at the time of the initial application.

However, data from SPRINT Phase II Stratum 1 showing an overall response rate (ORR) = 68.0% (34/50 participants; 95% CI, 53.3 – 80.5) in paediatric patients aged 3 to 18 years with NF1 who have symptomatic, inoperable plexiform neurofibromas PN can be extrapolated to patients aged 1 to < 3 years given that:

- The pathophysiology of NF1 is similar across patients aged ≥ 1 to ≤ 18 year. It is acknowledged that the aetiology of NF1 an autosomal dominant disorder due to pathogenic variants in the gene encoding for the NF1 tumour suppressor (17q11.2) is identical across all the paediatric

population. However, it is noted that growth of PNs occurs more rapidly in young children[2] which could be a source of bias

- The mechanism of action of selumetinib is the same.
- The ORR was similar across age groups in SPRINT Phase II Stratum 1 study. It can be assumed that the response rate will not be very different in patient aged 1 to < 3 years than in patients aged 3 to 7 years.

Wording of the indication:

Upon consideration by the CHMP, the use of the granule formulation of Koselugo in patients older than 7 years old with swallowing difficulties was also considered relevant, and the wording of the indication was proposed to be amended. The available efficacy data of the hard capsule formulation for patient aged 7 years and older from SPRINT and KOMET studies were considered supportive of amending the wording of the final indication.

Final wording of the indication - *Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in patients with neurofibromatosis type 1 (NF1) aged 1 year to less than 7 years and for older patients with swallowing difficulties.*

2.6.7. Conclusions on the clinical efficacy

From a clinical perspective no efficacy data were provided. However, data from paediatric patients aged 3 to 18 years can be extrapolated to patients aged 1 to < 3 years mainly based on PK data (see PK discussion) from study SPRINT Phase II Stratum 1. The available efficacy data of the hard capsule formulation for patient aged 7 years and older from SPRINT and KOMET studies were considered supportive of amending the wording of the final indication to include older patients with swallowing difficulties.

2.6.8. Clinical safety

The safety evaluation for the granule formulation of selumetinib at a dose equivalent to 25 mg/m^2 orally bid in paediatric patients with NF1 who have symptomatic inoperable PN who are aged ≥ 1 to < 7 years was based on the safety data from SPRINKLE study (D1346C00004).

Besides, the MAH also submitted a pooled safety dataset, also called NF1-PN Paediatric Pool that was generated to present cumulative safety data in the paediatric population with NF1 who have inoperable PN treated with selumetinib oral capsules. These were based on safety data from the following studies (details provided in section 2.6.1.): Study D1532C00057 (CTEP-sponsored SPRINT Phase I and SPRINT Phase II Stratum 1); Study D1346C00011 (Study 11); Study D1346C00013 (Study 13); Study D1346C00015 (Study 15).

The aim of the NF1-PN Paediatric Capsule Pool was to maximize the patient population to be able to calculate a more accurate estimation of the frequency of any AEs, and to be able to identify any rare AEs related to treatment that have not yet been observed.

Since the safety data from studies generating the NF1-PN pediatric Capsule Pool have been already assessed within the MAA process or in the context of P46 procedures, only data from SPRINKLE study

[2] Akshintala S, Baldwin A, Liewehr DJ, Goodwin A, Blakeley JO, Gross AM, et al. Longitudinal evaluation of peripheral nerve sheath tumors in neurofibromatosis type 1: Growth analysis of plexiform neurofibromas and distinct nodular lesions. Neuro Oncol 2020;22(9):1368-78.

will be evaluated. However, safety data from the NF1-PN pediatric Capsule Pool are presented as supportive data.

Safety data from studies including the adult population have been already assessed in the context of the MAA or in the context of type II variation and therefore not included in this section.

2.6.8.1. Patient exposure

Participant disposition in SPRINKLE was presented in the section 2.6.5.2.

Table 31. Participant Disposition for NF1-PN Pediatric Capsule Pool (On-selumetinib SAF)

	Number (%) of participants
	Selumetinib (N = 126)
Participants who received selumetinib	126 (100)
Participants ongoing on selumetinib at DCO date	45 (35.7)
Participants who completed selumetinib	39 (31.0)
Participants who prematurely discontinued selumetinib	42 (33.3)
AE	9 (7.1)
Complicating disease / intercurrent illness	2 (1.6)
Disease progression	11 (8.7)
Other	4 (3.2)
Physician decision	7 (5.6)
Protocol deviation	1 (0.8)
Participant decision	7 (5.6)
Switched to alternative treatment	1 (0.8)
Participants ongoing on study at DCO date	59 (46.8)
Participants who completed the study	41 (32.5)
Participants who prematurely discontinued the study	26 (20.6)
AE	1 (0.8)
Disease progression	5 (4.0)
Lost to follow-up	1 (0.8)
Other	7 (5.6)
Participant decision	8 (6.3)
Switched to alternative treatment	4 (3.2)

NF1-PN Pediatric Capsule Pool: SPRINT Phase I (DCO date: 27 Feb 2021) + SPRINT Phase II Stratum 1 (DCO: 31 Mar 2021) + pediatric cohort of D1346C00011 (DCO: 15 Aug 2023) + D1346C00013 (DCO: 23 Dec 2022) + D1346C00015 (DCO: 24 Apr 2023).

Table 32 Duration of Exposure for SPRINKLE (Safety Analysis Set)

Characteristic **Statistic**	**Total in study** **(N = 36)**
Duration of exposure (days) [a]	
Mean (SD)	354.7 (194.76)
Median (min, max)	329.5 (83, 771)

Characteristic Statistic	Total in study (N = 36)
Actual duration of exposure (days) [b]	
Mean (SD)	345.5 (191.74)
Median (min, max)	313.3 (83, 771)
Relative dose intensity (%) [c]	
Mean (SD)	97.9 (3.77)
Median (min, max)	100.0 (84, 100)

a. Duration of exposure = last dose date where dose > 0 mg or date of death if subject dies before end of treatment-first.

b. Actual duration of exposure = total exposure–total duration of dose interruptions. Dose interruption is defined as any days with dose = 0 mg and half days if planned frequency is twice per day, but actual frequency is once daily.

c. Relative dose intensity = 100% × d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the or the actual last day of dosing.

Table 33 Duration of Exposure for NF1-PN Pediatric Capsule Pool (On-selumetinib SAF)

Characteristic Statistic	Selumetinib (N = 126)
Total exposure (days) [a]	
Mean (SD)	1130.2 (729.28)
Median (min, max)	808.0 (28, 2941)
Total treatment days	142408
Total exposure periods, n (%) [a]	
< 12 months	8 (6.3)
≥ 12 - ≤ 24 months	46 (36.5)
> 24 - ≤ 36 months	22 (17.5)
> 36 months	50 (39.7)
Actual exposure (days) [b]	
Mean (SD)	1064.2 (681.79)
Median (min, max)	776.5 (26, 2908)
Total treatment days	134092
Actual exposure periods, n (%) [b]	
< 12 months	8 (6.3)
≥ 12 - ≤ 24 months	51 (40.5)
> 24 - ≤ 36 months	18 (14.3)
> 36 months	49 (38.9)

[a] Total exposure = min (last dose date where dose > 0 mg, date of death or DCO date) - first dose date + 1.

[b] Actual exposure = total exposure - total duration of dose interruptions.

NF1-PN Pediatric Capsule Pool: SPRINT Phase I (DCO date: 27 Feb 2021) + SPRINT Phase II Stratum 1 (DCO date: 31 Mar 2021) + pediatric cohort of D1346C00011 (DCO: 15 Aug 2023) + D1346C00013 (DCO: 23 Dec 2022) + D1346C00015 (DCO: 24 Apr 2023).

Total treatment days = sum of (total treatment duration of each patient).

2.6.8.2. Adverse events

Table 34. Overall Summary of AEs (participant count) by Exposure Periods in SPRINKLE vs NF1-PN Pediatric Capsule Pool (On-selumetinib SAF)

AE category	Number (%) of participants [a] [EAR (per 100 person-years)]			
	Exposure Period: 0-12 cycles		Exposure Period: 0 to DCO	
	SPRINKLE (N = 36) (PY = 26.3)	NF1-PN Pediatric Capsule Pool (N = 126) (PY = 112.8)	SPRINKLE (N = 36) (PY = 35.0)	NF1-PN Pediatric Capsule Pool (N = 126) (PY = 394.4)
Participants with any AE	36 (100) [136.9]	125 (99.2) [110.8]	36 (100) [102.9]	125 (99.2) [31.7]
Any AE related to selumetinib [b]	35 (97.2) [133.1]	121 (96.0) [107.3]	35 (97.2) [100.0]	122 (96.8) [30.9]
Any AE of CTCAE Grade 3 or higher	4 (11.1) [15.2]	45 (35.7) [39.9]	4 (11.1) [11.4]	64 (50.8) [16.2]
Any AE of CTCAE Grade 3 or higher, related to selumetinib [b]	2 (5.6) [7.6]	25 (19.8) [22.2]	2 (5.6) [5.7]	41 (32.5) [10.4]
Any AE with outcome of death	0	0	0	0
Any AE with outcome of death, related to selumetinib [b]	0	0	0	0
Any SAE (including events with outcome of death)	2 (5.6) [7.6]	15 (11.9) [13.3]	2 (5.6) [5.7]	29 (23.0) [7.4]
Any SAE (including events with outcome of death), related to selumetinib [b]	0	7 (5.6) [6.2]	0	11 (8.7) [2.8]
Any SAE leading to discontinuation of selumetinib	0	2 (1.6) [1.8]	0	4 (3.2) [1.0]
Any SAE leading to discontinuation of selumetinib, related to selumetinib [b]	0	2 (1.6) [1.8]	0	3 (2.4) [0.8]
Any AE leading to discontinuation of selumetinib	0	4 (3.2) [3.5]	0	9 (7.1) [2.3]
Any AE leading to dose interruption of selumetinib	11 (30.6) [41.8]	56 (44.4) [49.6]	11 (30.6) [31.4]	78 (61.9) [19.8]
Any AE leading to dose reduction of selumetinib	0	22 (17.5) [19.5]	0	35 (27.8) [8.9]
Any AE leading to dose modification [c]	11 (30.6) [41.8]	59 (46.8) [52.3]	11 (30.6) [31.4]	81 (64.3) [20.5]
Any AESIs	12 (33.3) [45.6]	85 (67.5) [75.4]	13 (36.1) [37.1]	95 (75.4) [24.1]
Any ADR	32 (88.9) [121.7]	123 (97.6) [109.0]	33 (91.7) [94.3]	124 (98.4) [31.4]
Any other significant AEs [d]	0	2 (1.6) [1.8]	0	4 (3.2) [1.0]

a Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories. EARs are defined as number of participants/100 PY. PY is the sum of all individual durations of exposure until treatment discontinuation or DCO of that exposure period, whichever comes first.
b As assessed by the investigator.
c Action taken either drug interruption and/or a dose reduction.
d Significant AEs, other than SAEs and those AEs leading to discontinuation of study intervention, which are of particular clinical importance, are identified/classified as other significant AEs.

Notes: Study D1346C00004 (SPRINKLE) DCO date: 08 Apr 2024.
NF1-PN Pediatric Capsule Pool: SPRINT Phase I (DCO date: 27 Feb 2021) + SPRINT Phase II Stratum 1 (DCO date: 31 Mar 2021) + pediatric cohort of D1346C00011 (DCO: 15 Aug 2023) + D1346C00013 (DCO: 23 Dec 2022) + D1346C00015 (DCO: 24 Apr 2023).
Exposure Period: 0-12 cycles (ie, the first 12 cycles of selumetinib exposure – class DCO = Day 336)
Exposure Period: 0-DCO (ie, overall selumetinib exposure until overall DCO date)

Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO.

Table 35. Adverse events experienced by ≥10% of total participants overall (safety analysis set)

System organ class Preferred term (MedDRA version 26.1)	Global Cohort 1 ≥ 4 to < 7 years) N = 15 n (%)	Global Cohort 2 (≥ 1 to < 4 years) N = 17 n (%)	Total in Global N = 32 n (%)	Japan Cohort (≥ 1 to < 7 years) N = 4 n (%)	Total in study N = 36 n (%)
Any AE	15 (100)	17 (100)	32 (100)	4 (100)	36 (100)
Infections and infestations	15 (100)	13 (76.5)	28 (87.5)	3 (75.0)	31 (86.1)
Folliculitis	5 (33.3)	4 (23.5)	9 (28.1)	0	9 (25.0)
Gastroenteritis	2 (13.3)	2 (11.8)	4 (12.5)	1 (25.0)	5 (13.9)
Nasopharyngitis	4 (26.7)	2 (11.8)	6 (18.8)	0	6 (16.7)
Paronychia	8 (53.3)	7 (41.2)	15 (46.9)	1 (25.0)	16 (44.4)
Rhinitis	2 (13.3)	4 (23.5)	6 (18.8)	0	6 (16.7)
Upper respiratory tract infection	4 (26.7)	7 (41.2)	11 (34.4)	3 (75.0)	14 (38.9)
Blood and lymphatic system disorders	2 (13.3)	7 (41.2)	9 (28.1)	0	9 (25.0)
Anaemia	2 (13.3)	6 (35.3)	8 (25.0)	0	8 (22.2)
Respiratory, thoracic and mediastinal disorders	4 (26.7)	8 (47.1)	12 (37.5)	0	12 (33.3)
Rhinorrhoea	1 (6.7)	3 (17.6)	4 (12.5)	0	4 (11.1)
Gastrointestinal disorders	11 (73.3)	15 (88.2)	26 (81.3)	3 (75.0)	29 (80.6)
Abdominal pain	3 (20.0)	2 (11.8)	5 (15.6)	0	5 (13.9)
Diarrhoea	6 (40.0)	7 (41.2)	13 (40.6)	1 (25.0)	14 (38.9)
Stomatitis	2 (13.3)	1 (5.9)	3 (9.4)	2 (50.0)	5 (13.9)
Vomiting	4 (26.7)	8 (47.1)	12 (37.5)	2 (50.0)	14 (38.9)
Skin and subcutaneous tissue disorders	14 (93.3)	16 (94.1)	30 (93.8)	3 (75.0)	33 (91.7)
Alopecia	2 (13.3)	6 (35.3)	8 (25.0)	0	8 (22.2)
Dry skin	9 (60.0)	8 (47.1)	17 (53.1)	0	17 (47.2)
Eczema	6 (40.0)	5 (29.4)	11 (34.4)	3 (75.0)	14 (38.9)
Hair colour changes	3 (20.0)	3 (17.6)	6 (18.8)	0	6 (16.7)
General disorders and administration site conditions	9 (60.0)	12 (70.6)	21 (65.6)	0	21 (58.3)
Fatigue	4 (26.7)	2 (11.8)	6 (18.8)	0	6 (16.7)
Pyrexia	7 (46.7)	10 (58.8)	17 (53.1)	0	17 (47.2)
Investigations	6 (40.0)	5 (29.4)	11 (34.4)	1 (25.0)	12 (33.3)
Aspartate aminotransferase increased	2 (13.3)	2 (11.8)	4 (12.5)	0	4 (11.1)
Blood creatine phosphokinase increased	5 (33.3)	5 (29.4)	10 (31.3)	1 (25.0)	11 (30.6)

Note: Based on DCO1 date 08 Apr 2024.

Included AEs with an onset or worsening date on or after the date of first selmetininb dose up to and including 30 days after the date of last selumetinib dose. Participants with multiple occurrences are counted once per SOC and PT regardless of the number of occurrences.

Table is sorted by international order for SOC and in alphabetical order for PT.

Source: Table 14.3.2.2 and Appendix 16.2.7.1

Table 36. Number of Participants with AEs (Occurring in ≥ 20% of Participants) by System Organ Class and Preferred Term in SPRINKLE vs NF1-PN Pediatric Capsule Pool by Exposure Periods (On-selumetinib SAF)

System organ class Grouped preferred term	Number (%) of participants	
	Exposure period: 0 to DCO	
	SPRINKLE (N = 36)	NF1-PN Pediatric Capsule Pool (N = 126)
Participants with any AE	36 (100)	125 (99.2)
Infections and infestations	31 (86.1)	102 (81.0)
Folliculitis	9 (25.0)	7 (5.6)
Paronychia	16 (44.4)	63 (50.0)
Upper respiratory tract infection	14 (38.9)	31 (24.6)
Blood and lymphatic system disorders	9 (25.0)	49 (38.9)
Anaemia	8 (22.2)	43 (34.1)
Metabolism and nutrition disorders	10 (27.8)	82 (65.1)
Hyperglycaemia	1 (2.8)	30 (23.8)
Hypoalbuminaemia	0	38 (30.2)
Nervous system disorders	4 (11.1)	68 (54.0)
Headache	2 (5.6)	55 (43.7)
Respiratory, thoracic and mediastinal disorders	12 (33.3)	78 (61.9)
Cough	3 (8.3)	45 (35.7)
Epistaxis	3 (8.3)	31 (24.6)
Nasal congestion	0	36 (28.6)
Oropharyngeal pain	0	35 (27.8)
Gastrointestinal disorders	29 (80.6)	111 (88.1)
Abdominal pain	5 (13.9)	43 (34.1)
Abdominal pain upper	2 (5.6)	37 (29.4)
Constipation	3 (8.3)	31 (24.6)
Diarrhoea	14 (38.9)	71 (56.3)
Nausea	2 (5.6)	66 (52.4)
Stomatitis	5 (13.9)	50 (39.7)
Vomiting	14 (38.9)	78 (61.9)
Skin and subcutaneous tissue disorders	33 (91.7) [94.3]	117 (92.9)
Alopecia	8 (22.2)	30 (23.8)
Dermatitis acneiform	1 (2.8)	69 (54.8)
Dry skin	17 (47.2)	56 (44.4)
Eczema	14 (38.9)	28 (22.2)
Pruritus	3 (8.3)	40 (31.7)
Rash maculo-papular	3 (8.3)	38 (30.2)
Musculoskeletal and connective tissue disorders	3 (8.3)	71 (56.3)

System organ class Grouped preferred term	Number (%) of participants Exposure period: 0 to DCO	
	SPRINKLE (N = 36)	NF1-PN Pediatric Capsule Pool (N = 126)
Back pain	0	27 (21.4)
Pain in extremity	1 (2.8)	28 (22.2)
General disorders and administration site conditions	21 (58.3)	85 (67.5)
Fatigue	6 (16.7)	47 (37.3)
Pyrexia	17 (47.2)	55 (43.7)
Investigations	12 (33.3)	99 (78.6)
Alanine aminotransferase increased	2 (5.6)	36 (28.6)
Aspartate aminotransferase increased	4 (11.1)	46 (36.5)
Blood creatine phosphokinase increased	11 (30.6)	68 (54.0)
Ejection fraction decreased	0	26 (20.6)
Lymphocyte count decreased	0	31 (24.6)
Neutrophil count decreased	1 (2.8)	33 (26.2)

Notes: Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

Study D1346C00004 (SPRINKLE) DCO date: 08 Apr 2024. NF1-PN Pediatric Capsule Pool: SPRINT Phase I (DCO date: 27 Feb 2021) + SPRINT Phase II Stratum 1 (DCO date: 31 Mar 2021) + pediatric cohort of D1346C00011 (DCO: 15 Aug 2023) + D1346C00013 (DCO: 23 Dec 2022) + D1346C00015 (DCO: 24 Apr 2023).

All pediatric studies used CTCAE V5.0, while SPRINT used CTCAE V4.03. MedDRA version 26.1. Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO.

Table 37. Frequency of ADRs SPRINKLE vs NF-PN Pediatric Capsule Pool (On-selumetinib SAF)

System organ class Grouped preferred term/ Preferred term	Number (%) of participants [a]			
	SPRINKLE (N = 36)		NF1-PN Pediatric Capsule Pool (N = 126)	
	All CTCAE Grades	CTCAE Grade ≥ 3 [b]	All CTCAE Grades	CTCAE Grade ≥ 3 [c]
Participants with any ADR	33 (91.7)	2 (5.6)	124 (98.4)	41 (32.5)
Eye disorders	1 (2.8)	0	11 (8.7)	0
Vision blurred	1 (2.8)	0	11 (8.7)	0
Respiratory, thoracic and mediastinal disorders	0	0	7 (5.6)	0
Dyspnoea [d]	0	0	7 (5.6)	0
Gastrointestinal disorders	21 (58.3)	0	102 (81.0)	21 (16.7)
Diarrhoea	14 (38.9)	0	71 (56.3)	13 (10.3)
Dry mouth	0	0	5 (4.0)	0
Nausea	2 (5.6)	0	66 (52.4)	2 (1.6)

System organ class Grouped preferred term/ Preferred term	Number (%) of participants [a]			
	SPRINKLE (N = 36)		NF1-PN Pediatric Capsule Pool (N = 126)	
	All CTCAE Grades	CTCAE Grade ≥ 3 [b]	All CTCAE Grades	CTCAE Grade ≥ 3 [c]
Stomatitis	5 (13.9)	0	50 (39.7)	1 (0.8)
Vomiting	14 (38.9)	0	78 (61.9)	9 (7.1)
Skin and subcutaneous tissue disorders	28 (77.8)	1 (2.8)	112 (88.9)	17 (13.5)
Dermatitis acneiform	1 (2.8)	0	69 (54.8)	3 (2.4)
Dry skin	17 (47.2)	0	56 (44.4)	1 (0.8)
Hair changes [d]	10 (27.8)	0	37 (29.4)	0
Paronychia	16 (44.4)	1 (2.8)	63 (50.0)	12 (9.5)
Rashes (non-acneiform) [d]	5 (13.9)	0	49 (38.9)	3 (2.4)
General disorders and administration site conditions	20 (55.6)	0	80 (63.5)	6 (4.8)
Asthenic events [d]	6 (16.7)	0	47 (37.3)	0
Facial oedema [d]	0	0	10 (7.9)	0
Peripheral oedema [d]	3 (8.3)	0	23 (18.3)	0
Pyrexia	17 (47.2)	0	55 (43.7)	6 (4.8)
Investigations	15 (41.7)	1 (2.8)	98 (77.8)	13 (10.3)
Alanine aminotransferase increased	2 (5.6)	0	36 (28.6)	3 (2.4)
Aspartate aminotransferase increased	4 (11.1)	0	46 (36.5)	2 (1.6)
Blood creatine phosphokinase increased	11 (30.6)	1 (2.8)	68 (54.0)	7 (5.6)
Blood albumin decreased [d]	0	0	44 (34.9)	0
Blood creatinine increased	1 (2.8)	0	24 (19.0)	1 (0.8)
Ejection fraction decreased	0	0	26 (20.6)	1 (0.8)
Haemoglobin decreased [d]	8 (22.2)	0	44 (34.9)	2 (1.6)
Increased blood pressure [d]	0	0	14 (11.1)	0

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

[b] All events were CTCAE Grade 3 (see Pediatric ISS Table 3.5.5.1)

[c] All events were CTCAE Grade 3, except for Grade 4 blood creatine phosphokinase increased in 2 participants and blood creatinine increased in 1 participant (see Pediatric ISS Table 3.5.5.1p)

[d] ADRs based on grouping of individual PT:

Rashes (non-acneiform): rash maculo-papular, rash papular, rash, rash erythematous, rash macular, rash pruritic

Hair changes: alopecia, hair colour change

Asthenic events: fatigue, asthenia

Peripheral oedema: oedema peripheral, oedema, localised oedema, peripheral swelling

Facial oedema: periorbital oedema, face oedema

Dyspnoea: dyspnoea exertional, dyspnoea, dyspnoea at rest

Increased blood pressure: hypertension, blood pressure increased

Haemoglobin decreased: anaemia, haemoglobin decreased

Blood albumin decreased: hypoalbuminaemia, blood albumin decreased

Notes: There were no deaths.

NF1-PN Pediatric Capsule Pool: SPRINT Phase I (DCO date: 27 Feb 2021) + SPRINT Phase II Stratum 1 (DCO date: 31 Mar 2021) + pediatric cohort of D1346C00011 (DCO: 15 Aug 2023) + D1346C00013 (DCO: 23 Dec 2022) + D1346C00015 (DCO: 24 Apr 2023).

Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO.

All pediatric studies used CTCAE V5.0, while SPRINT used CTCAE V4.03. MedDRA version 26.1

Table 38. Time to First Onset and Duration of Adverse Drug Reactions Occurring in ≥ 5% of Participants in SPRINKLE (On-selumetinib SAF)

Preferred term	Median time to first onset (days) [0]	Median duration (days) [b]	Led to dose interruption in number of participants
Vomiting	46.0	1.0	4
Pyrexia	44.0	3.0	4
Diarrhoea	27.5	5.5	2

[a] Each participant with an event was selected with earliest onset day with the max CTCAE grade.

[b.] If a participant had multiple AEs within the max CTCAE grade, all durations are summed. Duration was not calculated when the AE end date was missing.

Table 39. Time to Onset and Duration of Adverse Drug Reactions in NF1-PN Pediatric Capsule Pool (On-selumetinib SAF)

			Led to:		
Preferred term	**Median time to first onset (days) [d]**	**Median duration (days) [b]**	**Dose interruption in number of participants**	**Dose reduction in number of participants**	**Treatment discontinuation in number of participants**
Paronychia	375	55	18	9	1
Vomiting	106.5	3	25	0	0
Nausea	43	16	14	0	1
Diarrhoea	69	5.5	11	1	1
Pyrexia	276	4	8	0	0
Rashes (non-acneiform)	302	66.5	7	2	0
Vision blurred	820	117	2	0	0
Dry mouth	13	16.5	0	0	0
Stomatitis	144	38	6	2	1
Asthenic events	76	22	1	0	1
Facial oedema	245	42	0	0	0
Peripheral oedema	581	134.5	2	0	0
Alanine aminotransferase increased	186.5	71	1	2	0
Aspartate aminotransferase increased	139.5	198	1	2	0
Blood creatine phosphokinase increased	112	126	5	5	0

			Led to:		
Preferred term	**Median time to first onset (days) [d]**	**Median duration (days) [b]**	**Dose interruption in number of participants**	**Dose reduction in number of participants**	**Treatment discontinuation in number of participants**
Blood albumin decreased	157	96	0	0	0
Blood creatinine increased	141	173	0	0	1
Ejection fraction decreased	283	110	2	4	0
Haemoglobin decreased	279.5	233	1	0	0
Increased blood pressure	166.5	47.5	0	0	0
Dyspnoea	444	63.5	0	0	0
Dermatitis acneiform	28	176	4	3	0
Dry skin	140	173	2	0	0
Hair changes	113	267	1	0	0

d. Each subject with an event was selected with earliest onset day with the max CTCAE grade.

b. If a subject had multiple AEs within the max CTCAE grade, all durations are summed. Duration was not calculated when the AE end date was missing.

2.6.8.3. Serious adverse events, deaths, and other significant events

Serious adverse events (SAEs) in SPRINKLE study

Table 40. Number of subjects with serious adverse events, by system organ class and preferred term - by exposure periods Study D1346C00004

	Number (%) of subjects [exposure-adjusted rate (per 100 person-years)] [a]			
System organ class Grouped Preferred term	0-12 Cycles (N=36) PY = 26.3	>12-24 Cycles (N=18) PY = 8.0	>24 Cycles (N=4) PY = 0.6	0 to DCO (N=36) PY = 35.0
Subjects with any SAE	2 (5.6) [7.6]	0	0	2 (5.6) [5.7]
INFECTIONS AND INFESTATIONS	1 (2.8) [3.8]	0	0	1 (2.8) [2.9]
Gastroenteritis	1 (2.8) [3.8]	0	0	1 (2.8) [2.9]
Upper respiratory tract infection	1 (2.8) [3.8]	0	0	1 (2.8) [2.9]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (2.8) [3.8]	0	0	1 (2.8) [2.9]
Pyrexia	1 (2.8) [3.8]	0	0	1 (2.8) [2.9]

Study D1346C00004 DCO date: 08-Apr-2024.
Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO.
[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories. Exposure-adjusted rates = number of subjects/100 PY. PY is the sum of all individual exposure durations in the period until the earliest of treatment discontinuation or DCO of that exposure period.

SAEs in the safety pool

Table 41. Number of subjects with serious adverse events, by system organ class and preferred term - by exposure periods NF1-PN Paediatric Capsule Pool

	Number (%) of subjects [exposure-adjusted rate (per 100 person-years)] [a]			
System organ class Grouped Preferred term	0-12 Cycles (N=126) PY = 112.8	>12-24 Cycles (N=119) PY = 92.6	>24 Cycles (N=82) PY = 189.0	0 to DCO (N=126) PY = 394.4
Subjects with any SAE	15 (11.9) [13.3]	9 (7.6) [9.7]	9 (11.0) [4.8]	29 (23.0) [7.4]
INFECTIONS AND INFESTATIONS	6 (4.8) [5.3]	2 (1.7) [2.2]	4 (4.9) [2.1]	10 (7.9) [2.5]
Bacterial tracheitis	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
COVID-19	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Clostridium difficile colitis	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Influenza	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
Osteomyelitis	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
Paronychia	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Sepsis	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Skin infection	0	0	2 (2.4) [1.1]	2 (1.6) [0.5]
Urinary tract infection	2 (1.6) [1.8]	0	1 (1.2) [0.5]	2 (1.6) [0.5]
Vulval cellulitis	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
Neurofibrosarcoma	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.8) [0.9]	1 (0.8) [1.1]	0	2 (1.6) [0.5]
Anaemia	1 (0.8) [0.9]	1 (0.8) [1.1]	0	2 (1.6) [0.5]
METABOLISM AND NUTRITION DISORDERS	1 (0.8) [0.9]	1 (0.8) [1.1]	2 (2.4) [1.1]	3 (2.4) [0.8]
Dehydration	0	1 (0.8) [1.1]	2 (2.4) [1.1]	2 (1.6) [0.5]
Hyperkalaemia	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Hyperuricaemia	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Hypocalcaemia	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
PSYCHIATRIC DISORDERS	1 (0.8) [0.9]	1 (0.8) [1.1]	1 (1.2) [0.5]	2 (1.6) [0.5]
Depression	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Suicidal ideation	1 (0.8) [0.9]	1 (0.8) [1.1]	0	1 (0.8) [0.3]
NERVOUS SYSTEM DISORDERS	1 (0.8) [0.9]	0	1 (1.2) [0.5]	2 (1.6) [0.5]
Headache	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Loss of consciousness	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
VASCULAR DISORDERS	1 (0.8) [0.9]	1 (0.8) [1.1]	1 (1.2) [0.5]	3 (2.4) [0.8]
Haematoma	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Hypertension	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Hypotension	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.8) [1.1]	1 (1.2) [0.5]	2 (1.6) [0.5]

Hypoxia	0	1 (0.8) [1.1]	1 (1.2) [0.5]	2 (1.6) [0.5]
GASTROINTESTINAL DISORDERS	2 (1.6) [1.8]	1 (0.8) [1.1]	4 (4.9) [2.1]	6 (4.8) [1.5]
Abdominal pain	0	1 (0.8) [1.1]	2 (2.4) [1.1]	2 (1.6) [0.5]
Constipation	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Diarrhoea	2 (1.6) [1.8]	0	0	2 (1.6) [0.5]
Inguinal hernia	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Vomiting	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
Skin ulcer	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (0.8) [0.9]	0	1 (1.2) [0.5]	2 (1.6) [0.5]
Flank pain	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Scoliosis	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
RENAL AND URINARY DISORDERS	3 (2.4) [2.7]	0	0	3 (2.4) [0.8]
Acute kidney injury	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Haematuria	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Proteinuria	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
Torsion of the urethra	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.8) [0.9]	1 (0.8) [1.1]	1 (1.2) [0.5]	3 (2.4) [0.8]
Oedema peripheral	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Pyrexia	1 (0.8) [0.9]	1 (0.8) [1.1]	0	2 (1.6) [0.5]
INVESTIGATIONS	2 (1.6) [1.8]	1 (0.8) [1.1]	0	3 (2.4) [0.8]
Blood creatine phosphokinase increased	1 (0.8) [0.9]	1 (0.8) [1.1]	0	2 (1.6) [0.5]
Blood creatinine increased	1 (0.8) [0.9]	0	0	1 (0.8) [0.3]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	2 (1.7) [2.2]	2 (2.4) [1.1]	4 (3.2) [1.0]
Fracture	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Humerus fracture	0	0	1 (1.2) [0.5]	1 (0.8) [0.3]
Injury	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]
Multiple injuries	0	1 (0.8) [1.1]	0	1 (0.8) [0.3]

NF1-PN Pediatric Capsule Pool: SPRINT Phase I (DCO date: 27-Feb-2021) + SPRINT Phase II stratum 1 (DCO date: 31-Mar-2021) + pediatric cohort of D1346C00011 (DCO: 15-Aug-2023) + D1346C00013 (DCO: 23-Dec-2022) + D1346C00015 (DCO: 24-Apr-2023). Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO.
[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories. Exposure-adjusted rates = number of subjects/100 PY. PY is the sum of all individual exposure durations in the period until the earliest of treatment discontinuation or DCO of that exposure period.

Deaths

In the SPRINKLE study, as of the DCO1, there were no AEs with a fatal outcome reported.

In the NF1-PN safety pool, there were no AEs with a fatal outcome either while patients were on selumetinib or during the 30-day follow-up period. Two patients died in the SPRINT Phase II Stratum 1 study, both due to neurofibrosarcoma, both SAEs of neurofibrosarcoma after selumetinib treatment was terminated.

Adverse events of special interest

Table 42. Summary of AESI by Grouped Term and Preferred Term SPRINKLE (On-selumetinib SAF)

Grouped term Preferred term	Max CTCAE Grade			
	1	2	3	Total in Study
Any AESIs	-	-	-	13 (36.1)
Cardiac toxicity	1 (2.8)	0	0	1 (2.8)
Oedema peripheral	1 (2.8)	0	0	1 (2.8)
Hepatotoxicity	4 (11.1)	0	0	4 (11.1)
Alanine aminotransferase increased	2 (5.6)	0	0	2 (5.6)

Grouped term Preferred term	Max CTCAE Grade			
	1	2	3	Total in Study
Aspartate aminotransferase increased	4 (11.1)	0	0	4 (11.1)
Muscular toxicity	6 (16.7)	4 (11.1)	1 (2.8)	11 (30.6)
Blood creatine phosphokinase increased	6 (16.7)	4 (11.1)	1 (2.8)	11 (30.6)
Ocular toxicity	2 (5.6)	0	0	2 (5.6)
Photophobia	1 (2.8)	0	0	1 (2.8)
Vision blurred	1 (2.8)	0	0	1 (2.8)

Notes: Includes AESIs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose.

Participants with multiple occurrences are counted once per grouped term and PT regardless of the number of occurrences.

Table is sorted by grouped term and in alphabetical order for PT.

CTCAE version 5.0. MedDRA version 26.1.

Ejection fraction decreased

In the NF1-PN Paediatric Pool (N = 126), LVEF reduction (PT: ejection fraction decreased) was reported in 26 (21%) patients; among them, in 25 (19.8%) patients, the reported ADRs were CTCAE grade 2, and in 1 (0.8%) patient, the ADR reported was CTCAE grade 3. In 4 (3.2%) patients, LVEF decrease led to dose reduction and in 2 (1.6%) patients, LVEF decrease led to dose interruption. At the time of analysis, of the 26 patients, 20 patients were recovered. The median time to first occurrence of LVEF reduction was 283 days (median duration 110.5 days).

Ocular toxicity

In the NF1-PN Paediatric Pool (N = 126), CTCAE grade 1 and 2 events of blurred vision were reported in 11 (9%) patients. Two patients (1.6%) required dose interruption. At the time of analysis, of the 11 patients, 10 patients were recovered.

Paronychia

In the NF1-PN Paediatric Pool (N = 126), paronychia was reported in 63 (50%) patients. The median time to first onset of maximum grade paronychia adverse event was 375 days (approximately 12 months) and the median duration of events was 55 days (approximately 2 months). The majority (51 patients, 40.5% the NF1-PN Paediatric Pool) had a maximum CTCAE grade of 1 or 2. Grade ≥ 3 events occurred in 12 (10%) patients. Eighteen patients (14.3%) required dose interruption for adverse event of paronychia, and 9 patients (7.1%) had an AE of paronychia that led to dose reduction. In one patient (0.8%) the event led to treatment discontinuation.

Blood creatine phosphokinase (CPK) increase

ADRs of blood CPK elevation occurred in 68 (54%) patients in the NF1-PN Paediatric Pool (N = 126). The median time to first onset of the maximum CTCAE grade CPK increase was 112 days (approximately 4 months) and the median duration of the maximum CTCAE grade event was 126 days (approximately 4 months). The majority (61 cases, 48.4% of the NF1-PN Paediatric Pool) had maximum CTCAE grade event that was grade 1 or 2. A maximum CTCAE grade 3 events occurred in 5 (4%) patients, and CTCAE grade 4 event occurred in 2 (1.6%) patients. Five patients had an AE of blood CPK increase that led to treatment interruptions and required dose reduction.

Gastrointestinal toxicities

In the NF1-PN Paediatric Pool (N = 126), vomiting (78 patients, 62%), diarrhoea (71 patients, 56%), nausea (66 patients, 52%), and stomatitis (50 patients, 40%) were the most commonly reported gastrointestinal (GI) events. The majority of these cases were CTCAE grade 1 or 2. CTCAE grade ≥ 3 events were reported for diarrhoea (10%), vomiting (7%), nausea (2%) and stomatitis (1%). Dose modification was required in 25 (19.8%) patients with vomiting, 14 (11.1%) with nausea, 11 (8.7%) with diarrhoea, and 6 (4.8%) with stomatitis. One patient each reported an event of diarrhoea, nausea and stomatitis led to treatment discontinuation. Dose reduction had occurred in 1 patient with ADR of diarrhoea and in 2 patients with ADR of stomatitis. No CTCAE grade ≥ 4 events were reported.

Skin toxicities

In the NF1-PN Paediatric Pool (N = 126), acneiform rashes were observed in 76 (60%) patients [median time to onset 29 days; median duration of 176 days (approximately 6 months) for the maximum CTCAE grade event]. The majority (73 patients, 58% of the NF1-PN Paediatric Pool) of these reported ADRs with maximum CTCAE were grade 1 or 2. In 4 patients (3.2%), acneiform rashes led to dose interruption and 3 patients (2.4%) acneiform rashes led to dose reduction. CTCAE grade 3 events were reported in 3 (2.4%) patients. Other (non-acneiform) rashes were observed in 49 (39%) patients in the NF1-PN Paediatric Pool and were predominantly (46 patients, 36.5% of the NF1-PN Paediatric Pool) CTCAE grade 1 or 2.

Hair changes

In the NF1-PN Paediatric Pool (N=126), 37 (29%) patients experienced hair changes adverse event (reported as [PT: hair colour changes] in 21 patients (16.7%) and hair thinning [PT: alopecia] in 30 patients (23.8%)). All cases were CTCAE grade 1 (33 patients, 26.2%) or 2 (4 patients, 3.2%) and dose interruption was reported in 1 (0.8%) patient.

2.6.8.4. Laboratory findings

From laboratory (haematology, clinical chemistry) and other findings (notably vital signs, electrocardiogram, echocardiogram and ophthalmologic assessments), no new safety issues were identified.

Table 43. Select Hematology CTCAE Grade Change from Baseline to Worst CTCAE Grade On Treatment in SPRINKLE (Safety Analysis Set)

Parameter			Worst CTCAE grade on treatment n (%)				
Laboratory variable (SI unit)	**Nobs**	**Baseline CTCAE grade**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin (g/L) (Low)	36	0	16 (44.4)	8 (22.2)	6 (16.7)	0	0
		1	1 (2.8)	4 (11.1)	1 (2.8)	0	0
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Lymphocytes (10^9/L) (Low)	32	0	15 (46.9)	3 (9.4)	5 (15.6)	1 (3.1)	0
		1	0	1 (3.1)	0	0	0
		2	0	0	7 (21.9)	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Neutrophils (10^9/L)	32	0	25 (78.1)	2 (6.3)	0	1 (3.1)	0
		1	2 (6.3)	1 (3.1)	0	0	0
		2	1 (3.1)	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0

Notes: On-treatment assessments include assessments on or after the date of first dose of IP up to and including the earlier of 30 days following the date of last IP dose, or DCO. Baseline is the last non-missing value prior to administration of the first dose of IP. Percentages are based on Nobs. CTCAE version 5.0.

Nobs = Number of participants per cohort with a baseline value and at least one post-baseline value on treatment.

Table 44 Select Chemistry CTCAE Grade Change from Baseline to Worst CTCAE Grade On Treatment in SPRINKLE (Safety Analysis Set)

Parameter			Worst CTCAE grade on treatment n (%)				
Laboratory variable (SI unit)	**N**	**Baseline CTCAE grade**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Alanine aminotransferase (ukat/L)	36	0	24 (66.7)	10 (27.8)	2 (5.6)	0	0
		1	0	0	0	0	0
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Alkaline phosphatase (ukat/L)	36	0	30 (83.3)	4 (11.1)	1 (2.8)	1 (2.8)	0
		1	0	0	0	0	0

Parameter			Worst CTCAE grade on treatment n (%)				
Laboratory variable (SI unit)	**N**	**Baseline CTCAE grade**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Amylase (ukat/L)	36	0	26 (74.3)	6 (17.1)	1 (2.9)	1 (2.9)	0
		1	0	1 (3.2)	0	0	0
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Aspartate aminotransferase (ukat/L)	36	0	16 (44.4)	19 (52.8)	1 (2.8)	0	0
		1	0	0	0	0	0
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Creatine kinase (ukat/L)	36	0	12 (33.3)	16 (44.4)	7 (19.4)	1 (2.8)	0
		1	0	0	0	0	0
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0
Potassium (mmol/L) (High)	36	0	23 (63.9)	9 (25.0)	0	1 (2.8)	0
		1	2 (5.6)	1 (2.8)	0	0	0
		2	0	0	0	0	0
		3	0	0	0	0	0
		4	0	0	0	0	0

Notes: On-treatment assessments include assessments on or after the date of first dose of IP up to and including the earlier of 30 days following the date of last IP dose, or DCO. Baseline is the last non-missing value prior to administration of the first dose of IP. Percentages are based on Nobs. CTCAE version 5.0.

N = Number of participants per cohort with a baseline value and at least one post-baseline value on treatment.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Table 45. Adverse Events by Age in SPRINKLE (On-selumetinib SAF)

AE category	Number (%) of participants [a] Selumetinib (N = 36)		
	< 2 years (N = 7)	**2 to ≤ 3 years (N = 11)**	**> 3 years (N = 18)**
Any AE	7 (100)	11 (100)	18 (100)
Any AE related to study intervention [b]	6 (85.7)	11 (100)	18 (100)
Any AE of CTCAE Grade 3 or higher	1 (14.3)	1 (9.1)	2 (11.1)
Any AE of CTCAE Grade 3 or higher, related to study intervention [b]			
Any SAE (including events with outcome of death)			
Any AE leading to dose interruption of study intervention	4 (57.1)	3 (27.3)	4 (22.2)
Any AE leading to dose modification [c]	4 (57.1)	3 (27.3)	4 (22.2)
Any AESIs	1 (14.3)	5 (45.5)	7 (38.9)
Any ADR	6 (85.7)	10 (90.9)	17 (94.4)

[a] Participants with multiple events in the same category are counted only once in that category. Participants with events in more than one category are counted once in each of those categories.

[b] As assessed by the investigator.

[c] Action taken either drug interruption and/or a dose reduction.

Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO.

Personal data removed from table

2.6.8.7. Immunological events

None.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Safety related to drug-drug interactions and other interactions has been assessed during the initial marketing authorization application.

2.6.8.9. Discontinuation due to adverse events

No AEs led to discontinuation of selumetinib in SPRINKLE study.

Table 46. Number of Participants with AEs Leading to Treatment Discontinuation, by System Organ Class and Preferred Term for NF1-PN Pediatric Capsule Pool (On-selumetinib SAF)

	Number (%) of participants
System organ class Preferred term	**Selumetinib (N = 126)**
Participants with any AE leading to treatment discontinuation	9 (7.1)

	Number (%) of participants
System organ class Preferred term	**Selumetinib (N = 126)**
Infections and infestations	1 (0.8)
Paronychia	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.8)
Neurofibrosarcoma	1 (0.8)
Gastrointestinal disorders	3 (2.4)
Diarrhoea	1 (0.8)
Gastrooesophageal reflux disease	1 (0.8)
Nausea	1 (0.8)
Stomatitis	1 (0.8)
Skin and subcutaneous tissue disorders	1 (0.8)
Skin ulcer	1 (0.8)
Musculoskeletal and connective tissue disorders	1 (0.8)
Myalgia	1 (0.8)
Renal and urinary disorders	1 (0.8)
Acute kidney injury	1 (0.8)
General disorders and administration site conditions	1 (0.8)
Fatigue	1 (0.8)
Investigations	2 (1.6)
Blood creatinine increased	1 (0.8)
Weight increased	1 (0.8)

Adverse events leading to dose modifications (interruptions or reduction)

SPRINKLE study

No AEs led to selumetinib dose reduction.

Table 47. Adverse Events Leading to Dose Interruption, by System Organ Class and Preferred Term During (Safety Analysis Set) – SPRINKLE study

System organ class Preferred term	Total in study N = 36 n (%)
Any AE leading to interruption of selumetinib[a]	*11 (30.6)*
Infections and infestations	11 (30.6)
COVID-19	1 (2.8)
Cystitis	1 (2.8)
Gastroenteritis	2 (5.6)
Herpangina	1 (2.8)
Herpes simplex reactivation	1 (2.8)
Nasopharyngitis	1 (2.8)
Oral fungal infection	1 (2.8)
Paronychia	1 (2.8)

System organ class Preferred term	Total in study N = 36 n (%)
Pharyngitis streptococcal	1 (2.8)
Streptococcal infection	1 (2.8)
Upper respiratory tract infection	2 (5.6)
Viral infection	1 (2.8)
Gastrointestinal disorders	6 (16.7)
Abdominal pain upper	1 (2.8)
Aphthous ulcer	1 (2.8)
Diarrhoea	2 (5.6)
Nausea	1 (2.8)
Stomatitis	1 (2.8)
Vomiting	4 (11.1)
Skin and subcutaneous tissue disorders	2 (5.6)
Eczema	2 (5.6)
Renal and urinary disorders	1 (2.8)
Proteinuria	1 (2.8)
General disorders and administration site conditions	4 (11.1)
Pyrexia	4 (11.1)

Note: Based on DCO1 date 08 Apr 2024.
Included AEs with an onset or worsening date on or after the date of first selumetinib dose up to and including 30 days after the date of last selumetinib dose. Participants with multiple occurrences were counted once per SOC and PT regardless of the number of occurrences.

NF1-PN Paediatric Capsule Pool

A total of 78 (61.9%) participants had AEs leading to dose interruption. The most frequent (≥ 5% of participants) AEs leading to dose interruption were vomiting (25 [19.8%] participants), paronychia (18, 14.3%), nausea (14, 11.1%), diarrhea and influenza like illness (11, 8.7% each), COVID-19 (10, 7.9%), and pyrexia (8, 6.3%).

A total of 35 (27.8%) participants had AEs leading to dose reduction. The most frequent (> 5% of participants) AE leading to dose reduction was paronychia (9 [7.1%] participants).

2.6.8.10. Post marketing experience

The safety profile of selumetinib was summarized in the Periodic Benefit Risk Evaluation Report covering the period 10 October 2023 through to 09 April 2024. As of 09 April 2024, selumetinib has been approved for the treatment of pediatric patients with NF1 who have symptomatic, inoperable PN in 58 countries.

As of 09 April 2024, the cumulative world-wide post-approval patient exposure since launch is estimated to be 24745 PYs (based on the maximum estimated daily dose of 100 mg) and 82484 PYs (based on the minimum estimated daily dose of 30 mg).

2.6.9. Discussion on clinical safety

The assessment of selumetinib safety profile for the granule formulation of selumetinib at a dose equivalent to 25 mg/m^2 orally bid in paediatric patients with NF1 who have symptomatic inoperable PN

who are aged ≥ 1 to < 7 years is based on the data from the ongoing SPRINKLE study (Study D1346C00004, DCO 08 April 2024).

Additional safety data have been submitted covering the period between 08 April 2024 and 25 November 2024 (90 Day safety update or DSU) and at the time of the DCO of this 90-DSU, there was no change in the safety conclusions. The assessment of these data does not allow the identification of new safety issues.

This application was also supported by safety data from 4 additional paediatric studies in patients with NF1 and inoperable PN that formed the NF1-PN Paediatric Capsule Pool. The relevant information from the following studies : study D1532C00057 (SPRINT; phase I and phase II stratum 1 – assessed during the initial MAA EMEA/H/C/005244), Study D1346C00015 (assessed during the procedure EMEA/H/C/005244/II/0013) and study D1346C00015 DCO2 (study 15 - assessed during the procedure EMEA/H/C/005244/P46/007), study D1346C00011 (study 11 - assessed during the procedure EMEA/H/C/005244/P46/005), and study D1346C00013 (study 13 - assessed during the procedure EMEA/H/C/005244/P46/006) is also included in this assessment report and reflected in section 4.8 of the SmPC.

SPRINKLE safety data was not included in the NF1-PN Paediatric Capsule Pool because the duration of exposure in SPRINKLE was short compared with the studies in the NF1-PN Paediatric Capsule Pool.

Adverse events - SPRINKLE

In SPRINKLE study, all patients had at least 1 AE. Most (35 [97.2%] patients) had at least 1 AE that that was considered related to selumetinib, and the majority were grade 1 or grade 2 in severity. Four (11.1%) patients overall experienced AEs that were ≥ Grade 3 in severity 2 of the events were considered related to selumetinib. Two (5.6%) patients overall experienced SAEs and none were considered related to selumetinib by the investigator.

None of the patients died during the study and none had an AE leading to discontinuation of selumetinib.

Eleven (30.6%) patients had AEs leading to dose interruptions but no patients had AEs leading to dose reductions.

The most common AEs belonged to the SOC "Skin and subcutaneous disorders" (91.7%), "Infections and infestations" (86.1%), and "Gastrointestinal disorders" (80.6%).

The most common AEs by PT (≥ 20% in all patients) overall were pyrexia and dry skin (17 [47.2%] patients each), paronychia (16, 44.4%), upper respiratory tract infection, eczema, diarrhoea, and vomiting (14, 38.9% each), blood creatine phosphokinase increased (11, 30.6%), folliculitis (9, 25.0%) alopecia and anaemia (8, 22.2% each).

Overall, the AEs reported during SPRINKLE study are consistent with those observed in SPRINT phase I and II studies, the pivotal studies assessed in the frame of the Marketing Authorisation Application. The SmPC of Koselugo has been updated to reflect the new data.

Adverse drug reaction (ADRs)

In the SPRINKLE study, 25% of paediatric patients experienced an adverse event of folliculitis (n=9/36) which is considered noteworthy compared to the 7 patients who experienced folliculitis in the NF1-PN Paediatric Capsule Pool (n=7/126, 5.6%). The AE of folliculitis was considered related to selumetinib in 8 patients from SPRINKLE study. Even though no particular action was taken towards selumetinib, most of the paediatric patients recovered after receiving an additional treatment. Considering this information, the compatible time-to onset, and no confounders identified, there is at least a reasonable possibility of a causal relationship between selumetinib and folliculitis. Folliculitis has

been added in the list of adverse drug reaction in the section 4.8 of the SmPC under the preferred term "Rashes (acneiform)".

A total of 8 (22.2%) participants had adverse drug reaction (ADRs) leading to dose modification. The ADRs leading to dose modification that were reported in ≥ 5% of participants were vomiting and pyrexia (4 [11.1%] participants each), and diarrhoea (2, 5.6%). The rest of the ADRs leading to dose modification were reported in 1 participant each. All events led to dose interruption.

No ADRs led to discontinuation of selumetinib.

Adverse events of special interest

In the Sprinkle study, a total of 13 (36.1%) patients had at least 1 or more AESI (. The most frequently reported AESI were blood creatine phosphokinase increased (11 [30.6%] patients) and aspartate aminotransferase increased (4, 11.1%). One (2.8%) participant had CTCAE Grade 3 blood creatine phosphokinase increased; the event did not lead to discontinuation of selumetinib. All AESIs observed in SPRINKLE except photophobia are known ADRs of selumetinib AESI were identified for 13 (36.1%) patients overall (40.0% in Global Cohort 1, 35.3% in Global Cohort 2, and 25.0% in Japan Cohort). The most commonly reported AESI was blood creatine phosphokinase increased (11 [30.6%] patients overall). One participant had Grade 3 blood creatine phosphokinase increased that was considered related to selumetinib.

One patient experienced an adverse event of photophobia in SPRINKLE study that was considered related to the studied drug and 3 patients reported also this AEs in NF1-PN Paediatric Capsule Pool. The MAH further discussed the corresponding cases and it is agreed that current data are not sufficiently robust to establish any causal association between the adverse event of photophobia and selumetinib.

Overall, no new safety issues are identified from adverse events of special interest.

Other safety findings

From laboratory (haematology, clinical chemistry) and other findings (notably vital signs, electrocardiogram, echocardiogram and ophthalmologic assessments), no new safety issue were identified based on the provided data (data not shown).

Comparison between SPRINKLE and NF1-PN Paediatric Capsule Pool

Overall, the demographics, disease characteristics, and medical history were similar between SPRINKLE and the NF1-PN Pediatric Capsule Pool except for expected differences in age.

The overall safety profile of the selumetinib granule formulation in paediatric patients ≥ 1 to < 7 years of age represented in SPRINKLE is consistent with the known safety profile of the selumetinib capsule formulation in paediatric patients aged ≥ 3 to < 18 years with NF1 and symptomatic, inoperable PN. No new safety concerns were identified.

The percentage of participants with AEs was similar between SPRINKLE (100%) and the NF1-PN Pediatric Capsule Pool (99.2%) during both exposure periods.

The most frequent treatment-related AEs reported in both SPRINKLE and the NF1-PN Pediatric Capsule Pool included blood creatine phosphokinase increased, dry skin, diarrhea, and anemia. The most frequent treatment-related AEs reported in SPRINKLE and not in the NF1 PN Pediatric Capsule Pool were folliculitis and eczema.

The frequency of SAEs in the NF1-PN Pediatric Capsule Pool (29 [23.0%] participants) was higher compared with SPRINKLE (2, 5.6%). This is most likely due to the longer treatment duration in the NF1-PN Paediatric Capsule Pool. The SAEs reported in SPRINKLE and not in the NF1-PN Paediatric

Capsule Pool were gastroenteritis and upper respiratory tract infection (n = 1; both Grade 3 and non-treatment related).

No AESI were reported in SPRINKLE that were not observed in the NF1-PN Pediatric Capsule Pool.

As of the DCO1, there were no AEs with a fatal outcome in Sprinkle.

Two patients died in the SPRINT Phase II Stratum 1 study, both due to neurofibrosarcoma, both SAEs of neurofibrosarcoma after selumetinib treatment was terminated. Both cases were considered unlikely related to selumetinib treatment and probably related to the disease under investigation.

No participants in SPRINKLE had AEs leading to treatment discontinuation. In the NF1-PN Pediatric Capsule Pool, 9 (7.1%) participants had AEs that led to treatment discontinuation. No AE leading to treatment discontinuation occurred in > 1 participant in the NF PN Pediatric Capsule Pool.

The incidence of AEs leading to dose interruption was higher in the NF1-PN Pediatric Capsule Pool (78 [61.9%] participants), compared with SPRINKLE (11, 34.4%). This is most likely due to the longer treatment duration in the NF1-PN Pediatric Capsule Pool.

AEs leading to dose reduction were reported in the NF1-PN Pediatric Capsule Pool and not in SPRINKLE likely due to the longer duration of treatment in the NF1-PN Pediatric Capsule Pool.

A similar percentage of participants had ADRs in SPRINKLE and NF1-PN Pediatric Capsule Pool (91.7% and 98.4%, respectively). The most frequent ADRs (≥ 40% of participants) in both SPRINKLE and the NF1 PN Pediatric Capsule Pool were dry skin (17 [47.2%] participants and 56, 44.4%, respectively), paronychia (16, 44.4% and 63, 50.0%, respectively), and pyrexia (17, 47.2% and 55, 43.7%, respectively).

The ADRs leading to dose modification that were reported in ≥ 5% of participants in both SPRINKLE and NF1-PN Pediatric Capsule Pool were vomiting, pyrexia, and diarrhea. No new ADRs leading to dose modification were reported in SPRINKLE.

A longer median time to first onset of ADRs in ≥ 5% of participants was observed in the NF1 PN Pediatric Capsule Pool than in SPRINKLE. This could be due to various factors such as the shorter duration of treatment, the younger age participants, and the smaller sample size in SPRINKLE.

No clinically significant changes in hematology or chemistry laboratory values, vital signs were reported in SPRINKLE or any of the studies in the NF1-PN Pediatric Capsule Pool.

No clinically significant abnormal ophthalmologic, ECG or ECHO findings were reported in SPRINKLE or any of the studies in the NF1-PN Pediatric Capsule Pool.

The assessment of the PSURs submitted since the granting of the marketing authorisation in paediatric patients with NF1 who have symptomatic inoperable PN did not identify new safety concerns.

The safety data did not have an impact on the safety concerns listed in the RMP. Overall, the risks are adequately addressed in the SmPC and RMP.

2.6.10. Conclusions on clinical safety

The safety profile of selumetinib in the SPRINKLE study for the granule formulation in paediatric patients with NF1 who have symptomatic inoperable PN who are aged ≥ 1 to < 7 years and for older patients with swallowing difficulties remains consistent with the safety data assessed during the initial MA process and from post-marketing monitoring.

Overall, the AEs reported during SPRINKLE study are consistent with those observed in SPRINT phase I and II studies, the pivotal studies assessed in the frame of the Marketing Authorisation Application. The SmPC of Koselugo has been updated to reflect the new data.

The overall safety profile of the selumetinib granule formulation is consistent with the known safety profile of the selumetinib capsule formulation in patients with NF1 and symptomatic, inoperable PN.

2.7. Risk Management Plan

2.7.1. Safety concerns

From the version 4.1 (DLP 05/08/2024), the safety concerns are:

Table 48 Summary of safety concerns

Important identified risks	Left ventricular ejection fraction reduction
Important potential risks	Physeal dysplasia Ocular toxicity Myopathy Hepatotoxicity
Missing information	Long-term exposure (including long-term safety data on developmental toxicity in children)

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the following safety concerns are provided in Annex 4 of the RMP:

- Left ventricular ejection fraction reduction
- Physeal dysplasia
- Ocular toxicity
- Myopathy
- Hepatotoxicity.

Follow-up questionnaires will be used to facilitate the post-marketing safety data collection for case reports with AEs. The purpose is to collect additional information related to the patient's underlying disease, past medical history, potential risk factors, sequence of events, diagnosis, management and outcome of treatment-emergent AEs, which will allow for more accurate assessment of the post-marketing safety profile of selumetinib.

Summary of planned additional PhV activities from RMP

Table Part III.3.1: On-going and planned additional pharmacovigilance activities.

Table 49. Ongoing and planned additional pharmacovigilance activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. (Study D1346R00004) Ongoing	To characterise the long-term safety profile of selumetinib among paediatric patients with NF1-related PN in real world clinical practice.	Left ventricular ejection fraction reduction Physeal dysplasia Ocular toxicity Myopathy Hepatotoxicity Long-term exposure (including long-term safety data on developmental toxicity in children)	Protocol submission Annual progress reports Interim analysis Final report	13 August 2021 Q3 2024 Q3 2025 Q3 2026 Q3 2027 Q3 2025 31 March 2029

NF1, neurofibromatosis type 1; PN, plexiform neurofibromas; Q, quarter.

2.7.3. Risk minimisation measures

3.4.3.1 Routine Risk Minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern.

Table 50. Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Left ventricular ejection fraction reduction	Routine risk communication: SmPC sections 4.2, 4.4, 4.8. Routine risk minimisation activities recommending specific clinical measures: SmPC section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of LVEF reduction.
Physeal dysplasia	None
Ocular toxicity	Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 (ADR of RVO, RPED). Routine risk minimisation activities recommending specific clinical measures: SmPC section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of events.
Myopathy	There are no routine risk minimisation activities for myopathy.

Safety concern	Routine risk minimisation activities
	Routine risk communication: for CPK increases, which may be a precursor for the clinical outcome of myopathy is outlined below: SmPC Section 4.8.
Hepatotoxicity	There is no routine risk communication for hepatotoxicity. Routine risk communication: for ALT and AST increases that may be precursors for the clinical outcome of hepatotoxicity is outlined below: SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures: SmPC section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of ALT and AST increases.
Long-term exposure (including long-term safety data on developmental toxicity in children)	None.

ADR, adverse drug reaction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; LVEF, left ventricular ejection fraction; RPED, retinal pigment epithelial detachment; RVO, retinal vein occlusion; SmPC, Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 4.1 is acceptable. In the next regulatory opportunity, the MAH needs to update the RMP to include the final approved indication.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Koselugo (selumetinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and as it is approved under a conditional marketing authorisation. Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The final indication for Koselugo 5 mg and 7.5 mg granules in capsule for opening is:

Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in patients with neurofibromatosis type 1 (NF1) aged 1 year to less than 7 years and for older patients with swallowing difficulties.

3.1.2. Available therapies and unmet medical need

The currently approved selumetinib capsule formulation precludes administration in children with a BSA of < 0.55 m^2 or young children < 7 years who may have difficulty swallowing capsules. Consequently, since > 50% of PNs are diagnosed in early childhood (birth to < 3 years), younger children with NF1-PN continue to have a significant unmet need. Therefore, the MAH has developed an alternative age-appropriate granule formulation of selumetinib for treatment of paediatric patients aged ≥ 1 to < 7 years with NF1 who have symptomatic, inoperable PN and for older patients with swallowing difficulties.

On 18/09/2025, a positive opinion for the extension of indication of selumetinib capsule to adults was adopted by CHMP (EMA/VR/0000245231).

Ezmekly (mirdametinib), an oral selective MEK inhibitor, is approved in the EU since 17 July 2025 for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

3.1.3. Main clinical studies

The SPRINKLE study is an ongoing Phase I/II, single arm, open-label study in children aged ≥ 1 to< 7 years at study entry with a clinical diagnosis of NF1 with symptomatic, inoperable PN. The study was designed to define the dose regimen and evaluate the PK, safety, and tolerability of selumetinib given as a granule formulation.

The MAH provided data from an interim analysis that did not include efficacy data. However data from SPRINT Phase II Stratum 1 showing an overall response rate (ORR) = 68.0% (34/50 participants; 95%

CI, 53.3 – 80.5) in paediatric patients aged 3 to 18 years with NF1 who have symptomatic, inoperable plexiform neurofibromas PN can be extrapolated to patients aged 1 to < 3 years.

3.2. Favourable effects

Efficacy data from SPRINT Phase II Stratum 1 showing an overall response rate (ORR) = 68.0% (34/50 participants; 95% CI, 53.3 – 80.5) in paediatric patients aged 3 to 18 years with NF1 who have symptomatic, inoperable plexiform neurofibromas PN can be extrapolated to patients aged 1 to < 3 years given that the pathophysiology of NF1 is similar across patients aged ≥ 1 to ≤ 18 year, the mechanism of action of selumetinib is the same and the ORR was similar across age groups in SPRINT Phase II Stratum 1 study.

Extrapolation of efficacy to patients aged 1–<3 years was supported by comparative PK analyses, showing that mean AUCss values in this age group fell within the efficacy range defined in SPRINT, with only modest differences compared to older children.

The granule formulation achieves comparable systemic exposure AUC levels but 30% to 35% lower Cmax compared to the capsule formulation. Given that AUC, rather than Cmax, is the key PK parameter driving clinical efficacy for selumetinib, it is agreed that the granule formulation does not negatively impact in vivo performance.

3.3. Uncertainties and limitations about favourable effects

No efficacy data have been provided in patients below 3 years of age however extrapolation based on PK data is considered acceptable.

Uncertainty remains due to the limited size and age distribution of the SPRINKLE PK dataset (n=10, including only one patient aged <2 years) and the untested nature of the proposed 25% posology increase in the lowest BSA subgroup. These limitations underline the residual uncertainty about exposure matching in the youngest patients and support the need for a stepwise dosing recommendation.

3.4. Unfavourable effects

The overall safety profile of the selumetinib granule formulation in pediatric participants ≥ 1 to < 7 years of age represented in SPRINKLE is consistent with the known safety profile of the selumetinib capsule formulation in pediatric participants aged ≥ 3 to < 18 years with NF1 and symptomatic, inoperable PN.

No clinically meaningful differences in AE frequencies were noted between SPRINKLE and the NF1-PN Paediatric Capsule Pool. The majority of AEs were considered related to study drug in both SPRINKLE and NF1-PN Paediatric Capsule.

The safety profile of selumetinib in the pediatric population with NF1 and inoperable PN is consistent with the known AE profile in adult cancer patients treated with selumetinib, as well as the MEK inhibitor class in general.

The majority of AEs reported with selumetinib were manageable with either selumetinib dose modifications and/or supportive therapy. Most resolved during the course of the studies and generally did not result in treatment discontinuation. The majority of the ADRs appear to occur in the first year of selumetinib treatment. The long-term tolerability of selumetinib is manageable. No change in the selumetinib safety profile was seen and no new safety concerns were observed after the addition of

Study 11, Study 13, and Study 15 to the original SPRINT data; ie, the safety profile of the NF1-PN Pediatric Capsule Pool is consistent with the safety data seen in SPRINT.

In the SPRINKLE study, the AE of folliculitis was considered related to selumetinib in 8 patients from SPRINKLE study. Even though no particular action was taken towards selumetinib, most of the paediatric patients recovered after receiving an additional treatment. Considering this information, the compatible time-to onset, and no confounders identified, there is at least a reasonable possibility of a causal relationship between selumetinib and folliculitis. Folliculitis has been added in the list of adverse drug reaction in the section 4.8 of the SmPC under the preferred term "Rashes (acneiform)".

No other new ADRs were identified during review of SPRINKLE safety data in paediatric clinical study participants treated with selumetinib granule formulation, and the pattern of ADRs observed was similar to those listed in section 4.8 of the SmPC of Koselugo.

3.5. Uncertainties and limitations about unfavourable effects

Long term developmental toxicity in children is considered as missing information in the RMP and a non-interventional PASS has been imposed in the context of the initial marketing authorization to further characterize this missing information. The final report is expected by 31 March 2029.

3.6. Effects Table

N/A

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy data from SPRINT Phase II Stratum 1 showed an overall response rate (ORR) = 68.0% (34/50 participants; 95% CI, 53.3 – 80.5) in paediatric patients aged 3 to 18 years with NF1 who have symptomatic, inoperable plexiform neurofibromas PN. The pathophysiology of NF1 is similar across patients aged ≥ 1 to < 18 year and the mechanism of action of selumetinib is the same and the ORR was similar across age groups in SPRINT Phase II Stratum 1 study. The extrapolation of efficacy to patients aged 1–<3 years is endorsed, however, in order to address the remaining uncertainties regarding the adequacy of the Pop-PK model and the lack of clinical testing of this adjustment, a stepwise dosing recommendation in section 4.2 of the SmPC is proposed.

The available efficacy data of the hard capsule formulation for patient aged 7 years and older from SPRINT and KOMET studies were considered supportive for amending the wording of the final indication for the Koselugo 5 mg and 7.5 mg, Granules in capsules for opening, to include older patients with swallowing difficulties.

The assessment of safety data from SPRINKLE study did not identify new safety concerns.

3.7.2. Balance of benefits and risks

The PK of the new proposed granule formulation of selumetinib has been sufficiently characterised and achieved overall comparable systemic exposure levels to those observed with the approved capsule formulation.

Efficacy data from SPRINT Phase II Stratum 1 in paediatric patients aged 3 to 18 years with NF1 who have symptomatic, inoperable plexiform neurofibromas PN can be reasonably extrapolated to patients aged 1 to < 3 years, given that the pathophysiology of NF1 is similar across patients aged ≥ 1 to ≤ 18 year, the mechanism of action of selumetinib is the same and the ORR was similar across age groups in SPRINT Phase II Stratum 1 study.

Considering the remaining uncertainties regarding the adequacy of the Pop-PK model and the lack of clinical testing of this adjustment, a stepwise dosing recommendation in SmPC section 4.2 is proposed and is considered appropriate.

The overall safety profile of the selumetinib granule formulation, including paediatric patients ≥ 1 to < 7 years of age represented in SPRINKLE and older patients with swallowing difficulties, is consistent with the known safety profile of the selumetinib capsule formulation in patients with NF1 and symptomatic, inoperable PN. No new safety concerns were identified.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall benefit/risk balance of Koselugo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Koselugo is not similar to Ezmekly within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Koselugo5 mg and 7.5 mg, Granules in capsules for opening is favourable in the following indication(s):

Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in patients with neurofibromatosis type 1 (NF1) aged 1 year to less than 7 years and for older patients with swallowing difficulties.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Koselugo subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive

2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0134/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		**Type**	**Annexes affected**
X.02.IV	Annex I_2.(d) Change or addition of a new pharmaceutical form	Line Extension	I, II, IIIA, IIIB and A
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, II, IIIA, IIIB and A
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA, IIIB

Extension application to introduce a new pharmaceutical form (Granules in capsules for opening) associated with new strengths (5 mg and 7.5 mg capsule) grouped with a Type II variation (C.I.4) to update sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Koselugo Capsules in order to align with the SmPC of Koselugo granules in capsules for opening. The Package Leaflet and Labelling are updated accordingly. The new presentations are indicated for the treatment of symptomatic, inoperable plexiform neurofibromas in patients with neurofibromatosis type 1 aged 1 year to less than 7 years and for older patients with swallowing difficulties. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and implement minor editorial changes.