18 September 2025
EMADOC-1700519818-2387194
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Koselugo

International non-proprietary name: Selumetinib

Procedure No. EMA/VR/0000245231

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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List of abbreviations

Abbreviation or Special Term	Explanation
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALAG1	absorption lag time
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AriMean	arithmetic mean
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration
AUC_{0-12}	area under the plasma concentration time curve from 0 to 12 hours
$AUC_{0-12,ss}$	area under the concentration-time curve from zero to 12 hours at steady state
AUC_{0-6}	area under the plasma concentration time curve from 0 to 6 hours
AUC_{0-8}	area under the plasma concentration time curve from 0 to 8 hours
AUC_{0-inf}	area under the plasma concentration time curve from 0 extrapolated to infinity
AUC_{0-t}	area under the plasma concentration time curve from 0 to the time of the last quantifiable concentration
AUC_{day}	area under the curve on the day of adverse event
AUC_{last}	area under the plasma concentration time curve from the time of dosing to the time of the last measurable (positive) concentration
AUC_{ss}	area under the curve at steady state
BALB	baseline albumin
bid	twice daily
bid	twice daily
BLQ	below the lower limit of quantification
BOR	best overall response
BSA	body surface area
CGIC	Clinical Global Impression of Change
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL/F	apparent clearance
CLm	clearance of metabolite
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration (at steady state)
COA	clinical outcome assessment

Abbreviation or Special Term	Explanation
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
cPR	confirmed partial response
CR	complete response
CSP	clinical study protocol
CSR	central serous retinopathy
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTD	common technical document
CTEP	Cancer Therapy Evaluation Program
CV	coefficient of variation
CYP	Cytochrome P450
D1	duration of zero-order selumetinib absorption
DCO	data cut-off
DCOA	Division of Clinical Outcome Assessment
DoR	duration of response
eCDF	empirical cumulative distribution function
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EoT	End of Treatment
EQ-5D-5L	EuroQol 5-Dimension 5-level
EQ-VAS	European Quality of Life Visual Analog Scale
ERK	extracellular signal-regulated kinase
ETA	Inter-individual random effects
EU	European Union
F1	bioavailability
FAS	Full Analysis Set
FDA	Food and Drug Administration
Fm	fraction metabolized
FPI	First participant in
GCP	Good Clinical Practice
gCV%	geometric coefficient of variation
GGT	gamma-glutamyl transferase
Gmean	geometric mean
gSD	geometric standard deviation
HPLC	high performance liquid chromatography

Abbreviation or Special Term	Explanation
HQC	high quality control
HRQoL	health-related quality of life
ICR	independent central review
IOP	intraocular pressure
IPD	important protocol deviation
IRT	Interactive Response Technology
ISE	Integrated Summary of Efficacy
ISR	incurred sample reanalysis
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
Ka	first-order absorption rate constant
LLOQ	lower limit of quantification
LOESS	locally weighted scatterplot smoothing
LPD	last participant dosed
LPI	last participant in
LPLV	last participant last visit
LQC	low quality control
LS	least squares
LSI	last subject in
LSLV	last subject last visit
LVEF	left ventricular ejection fraction
MAA	Marketing Authorization Application
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen activated protein kinase
Min	minimum
MMRM	mixed-effect model for repeated measures
MPAUC	metabolite-parent ratio based on AUC
MPC_{max}	metabolite-parent ratio based on C_{max}
MPNST	malignant peripheral nerve sheath tumours
MQC	medium quality control
MRI	magnetic resonance imaging
MS/MS	mass spectrometry
MSD	meaningful score difference
MTP	multiple testing procedure
n	number
NA	not applicable
NC	not calculated
NC	not calculated
NCA	Noncompartmental analysis

Abbreviation or Special Term	Explanation
NCI	National Cancer Institute
ND	not determined
NDA	New Drug Application
NDA	New Drug Application
NE	not evaluable
NF1	neurofibromatosis type 1
NIH	National Institutes of Health
NOMMEM	nonlinear mixed effects modelling
NQ	not quantifiable
NRS	numeric rating scale
NRS-11	Numerical Rating Scale 11
OAT3	organic anion transporter 3
On-Selumetinib SAF	enrolled participants who received any amount of selumetinib in the On-selumetinib Period
ORR	objective response rate
PAINS-pNF	Pain Intensity Scale for plexiform neurofibromas
PAP	psychometric analysis plan
PBRER	Periodic Benefit-Risk Evaluation Report
pcVPC	prediction-corrected visual predictive check
PD	progressive disease
PedsQL	Paediatric Quality of Life Inventory
pERK	phosphorylated extracellular signal-regulated kinase
PFS	progression free survival
PGIC	Patient's global impression of change
PII	Pain Interference Index
PII-pNF	Pain Interference Index – plexiform neurofibroma
PK	pharmacokinetic(s)
PlexiQoL	Plexiform Neurofibroma Quality of Life scale
PN	plexiform neurofibroma
PopPK	population pharmacokinetics
PR	partial response
Principal investigator	The investigator who leads the study conduct at an individual study center. Every study center has a principal investigator.
PRO	Patient Reported Outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	Preferred Term
PTAP	Post-trial access program
PY	person-years
Q	inter-compartmental selumetinib clearance
QC	quality control

Abbreviation or Special Term	Explanation
QoL	quality of life
QTcF	QTc interval as corrected by Fridericia's formula
Rac	accumulation ratio
RAF	proto-oncogene serine/threonine-protein kinase
Randomized Period SAF	enrolled participants who received any amount of study intervention during the Randomized Period
RAS	reticular activating system
RDI	relative dose intensity
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
RPED	retinal Pigment Endothelial Detachment
RSE	relative standard error
RVO	retinal vein occlusion
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMQ	Standardised MedDRA query
SOC	System Organ Class
SRC	Safety Review Committee
ss	steady state
$t_{1/2}$	half-life
TCP	temporal change parameter
TEAE	treatment-emergent adverse event
t_{last}	time of last observed concentration
t_{max}	time to reach maximum concentration
t_{max}	time to maximum plasma concentration
TPGS	Vitamin E polyethylene glycol succinate
TRAE	treatment-related adverse event
TTO	time to onset
TTP	time to progression
TTR	time to response
ULN	upper limit of normal
uPR	unconfirmed partial response
V2	selumetinib volume of distribution of central compartment
V3	selumetinib volume of distribution of peripheral compartment
Vss/F	volume of distribution (apparent) at steady state following extravenous administration
WRO	Written response only
λ_z	elimination rate constant

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 13 January 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication for KOSELUGO to include treatment of adults based on results from study D134BC00001 (KOMET). This is a phase III, multicentre, international study with a parallel, randomised, double-blind, placebo-controlled, 2 arm design that assesses efficacy and safety of selumetinib in adult participants with NF1 who have Symptomatic Inoperable Plexiform Neurofibromas. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC. As part of the application the MAH is requesting a 1-year extension of the market protection.

Information relating to orphan designation

Koselugo was designated as an orphan medicinal product EU/3/18/2050 on 31 July 2018. Koselugo was designated as an orphan medicinal product in the following indication:

Treatment of neurofibromatosis type 1.

Information on paediatric requirements

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

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

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. The request was withdrawn during the procedure.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Not applicable

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 25 February 2021 (EMA/SA/0000048622). The Protocol Assistance pertained to the following clinical aspects of the dossier:

- Phase 3 study design to demonstrate benefit/risk for the treatment of adult patients with NF1 and symptomatic plexiform neurofibromas: efficacy endpoints, targeted effect size, statistical analysis, study population, nested design with landmark analysis, duration of placebo-controlled period, methodology relating to the additional secondary endpoints including pain palliation and pain medication use, development of a new pain PRO, safety monitoring

The MAH received Protocol Assistance from the CHMP on 25 January 2024 (EMA/SA/0000159002). The Protocol Assistance pertained to the following clinical aspects of the dossier:

- Key secondary endpoint in the KOMET study for the purpose of measuring chronic target PN pain intensity

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Alexandre Moreau

Timetable	Actual dates
Submission date	13 January 2025
Start of procedure:	26 January 2025
CHMP Rapporteur's preliminary assessment report circulated on:	21 March 2025
PRAC Rapporteur's preliminary assessment report circulated on:	28 March 2025
PRAC outcome	10 April 2025
Updated CHMP (Joint) Rapporteur's updated assessment report circulated on:	16 April 2025
Request for supplementary information (RSI)	25 April 2025
MAH's responses submitted to the CHMP on	16 July 2025
Re-start of procedure	21 July 2025
CHMP Rapporteur Assessment Report	19 August 2025
PRAC Rapporteur Assessment Report	22 August 2025
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	4 September 2025

Timetable	Actual dates
Updated CHMP Rapporteur Assessment Report	11 September 2025
Opinion	18 September 2025
The CHMP adopted a report on similarity of Koselugo with Ezmekly on: (Appendix 1)	18 September 2025

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

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.

State the claimed the therapeutic indication

Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and older.

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).

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.

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).

Management

At the time of the initial submission of this variation, selumetinib was the only product approved for the treatment of symptomatic inoperable PNs in paediatric patients with NF1 from 3 years of age. However, Ezmekly (mirdametinib) was authorised in July 2025 for the treatment of plexiform neurofibromas (PN) in adults and children from 2 years of age with neurofibromatosis type 1 (NF1).

There is currently one systemic treatment option approved for patients with NF1 PN: Ezmekly (mirdametinib), an oral selective MEK inhibitor, approved in the EU in 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.

2.2.1. The development programme/compliance with CHMP guidance/scientific advice

Other key interactions that occurred during the design of KOMET and its suitability for the current application are summarized below:

Summary of Key Regulatory Interactions

Meeting Type, Date	Key Meeting Outcomes
FDA Type B (EOP), 15 Dec 2020	The FDA generally agreed with the Phase 3 study design, the endpoints, and the proposed validation plan for PRO instrument. The FDA recommended to limit the study to adult patients with symptomatic and "inoperable" PN and requested AstraZeneca to submit a draft SAP for review and have a follow-up discussion with the Agency on the SAP.
EMA CHMP Scientific Advice 25 Feb 2021 (EMA/SA/0000048622)	The CHMP provided advice on the proposed adult Phase 3 study design. In relation to the target population and inclusion criteria, it was agreed to limit the study to adult patients with symptomatic and "inoperable" PN. A placebo control was recommended although the initially suggested 32-week duration of the randomized, placebo-controlled assessment of ORR was considered too short and recommendation was made that this was extended. The pain endpoint was discussed and generally accepted. Advice was given on the assessment of chronic versus spike pain, and the potential confounding effects of pain medication.
FDA Type C, 17 Jun 2021	The FDA generally agreed with the SAP but recommended a formal hypothesis test comparing ORR at the end of Cycle 8 (prior to crossover)

Summary of Key Regulatory Interactions

Meeting Type, Date	Key Meeting Outcomes
	between the experimental and the control arm and did not consider the proposed MTP to be applicable.
FDA Type C, WRO 04 Mar 2022	FDA generally agreed on the elements of the study design but requested additional justification for the length of the placebo period with regards to patient pain control and for not considering crossover for clinical signs of progression. FDA generally agreed with the use of pain as a key secondary endpoint but suggested increasing the frequency of assessments using PROMIS, PedsQL, and PlexiQoL to include Cycles 6 and 10 and demonstrate that reductions in pain are not due to commensurate increases in analgesic use, and to also provide a plan for including diverse representation. FDA recommended using a MMRM rather than ANCOVA for the SAP regression model and to prespecify collection of PRO data regardless of whether a patient experiences disease progression or discontinues treatment. Additional comments regarding clinical pharmacology and DCOA would be forthcoming.
FDA Type B, 05 Dec 2023	The FDA asked for clarification of the missing data rules. The FDA recommended a missing data simulation study in the PAP and 2 efficacy supplemental analyses to evaluate chronic pain for the KOMET PAINS-pNF pain scale validation. Additionally, FDA requested specification of the definition and calculation of the chronic pain endpoint in the protocol and statistical analysis plan. The FDA also recommended that the meaningful change analyses be conducted, and the proposed MSD estimates be submitted prior to data unblinding. Within the meeting minutes, the FDA also provided the clinical pharmacology and DCOA feedback that was forthcoming after the 04 Mar 2022 Type C WRO. The Agency provided some comments on the PK sampling plan, exposure-response analyses, and PK-PD analysis for potential integration into the KOMET study or other ongoing studies to support the KOSELUGO development program, if feasible.
EMA CHMP Scientific Advice 25 Jan 2024 (EMA/SA/0000159002)	The CHMP considered PAINS-pNF chronic pain score fit-for-purpose as key secondary analysis of chronic target PN pain intensity in NF1-pNF. The psychometric analysis plan for the PAINS-pNF chronic pain based on the KOMET study was considered conventional and acceptable. There was no objection to use data of the KOMET study for the purpose of validation of the 2 newly developed endpoints i.e., PN-specific pain interference (PII-pNF) and NF1PN-specific spike pain.

2.2.2. General comments on compliance with GCP

Regarding GCP, the Applicant states that the Applicant's procedures, internal quality control measures and audit programmes provide reassurance that the clinical study program was carried out in accordance with GCP, as documented by the International Council for Harmonisation.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

A new ERA (25/11/2024) was submitted in this application. Only the introduction that explained the context of the variation is different from the ERA which was assessed in the extension of Koselugo in paediatric children with a new paediatric formulation (granules) from 1 to 7 years. As mentioned in this extension, the ERA is based on the NF1 population (all class of ages). Therefore, the conclusions are still valid. The Applicant has performed a Phase I and Phase II A and B, this ERA has been updated based on the current guideline published in September 2024.

To be noticed, according to the revised guideline on the environmental risk assessment (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr., 2024) the PNECgroundwater is based on the PNECsurface water and an additional AF of 10. If the PNECsw = 34 µg/L is divided by 10, the result is PNECgw = 3.4 µg/L and this value should be used for the risk calculation. In addition, with regard to the PECsediment, the conversion to µg/kg was rounded off too much. The PNEC is actually 1330 µg/kg dry weight. Even if this has no impact on the conclusions, it has been corrected in the ERA table.

Table 1: 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.

2.3.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of selumetinib:

- Considering the above data, selumetinib is not expected to pose a risk to the environment.

Apart from the ERA, no new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

	D1346C00011 (study 11)	KOMET
Type of study	PK, safety, and tolerability	Efficacy and safety
Study identifier	D1346C00011 (China PK study in adult and paediatric participants) NCT04590235	Study D134BC00001 (KOMET) NCT04924608 EudraCT number: 2020-005607-39 / 2023-507336-20-00 Refer to the primary CSR (DCO: 05 Aug 2024)
Objective(s) of the study	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 paediatric and adult participants with NF1 and inoperable PN.	Primary: To compare the effect of selumetinib relative to placebo by assessment of confirmed partial and complete response rate by end of Cycle 16 using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN.
Study design and type of control	This was an open-label, single-arm Phase I study with 2 independent	Phase III, randomized (1:1, with randomization stratified by average baseline

	cohorts to assess the safety, tolerability, PK, and clinical efficacy of selumetinib.	PAINS-pNF chronic target PN pain score and geographical region), double-blind, 2-arms (selumetinib and placebo) parallel-group, multicenter international study to evaluate the safety, efficacy, and PK of selumetinib administered orally compared to placebo in adult participants with NF1 who have symptomatic, inoperable PN.
Test product(s), dosage regimen, **route of administration**	25 mg/m^2 selumetinib (single dose) orally at Cycle 0. 25 mg/m^2 selumetinib bid orally (multiple doses) from Cycle 1 (28-day cycle). The dosage was adjusted for changes in body surface area according to the nomogram.	25 mg/m2 bid orally selumetinib (based on BSA, capped at 50 mg bid when BSA is ≥ 1.90 m2. in 28-day cycles until a selumetinib discontinuation criterion is met.
No. of participants randomized/ **treated**	32[a] (16 adult and 16 paediatric participants).	145[a] (selumetinib: 71; placebo: 74)
Healthy subjects or diagnosis of participants	Chinese paediatric and adult participants with NF1 and inoperable PN that required treatment due to symptoms or had the potential to develop significant clinical complications.	Adult participants with NF1 who have symptomatic, inoperable PN.
Duration of treatment	Following the screening period (Day -28 to Day -1), all eligible participants received a single oral dose of selumetinib (Cycle 0). After a 2-day period following the single dose, participants received oral doses of selumetinib bid continuously for 28-day cycles starting at Cycle 1. Participants continued to receive selumetinib until progressive disease based on the Investigator's decision or unacceptable drug-related toxicity, whichever occurred first.	During the Randomized Period participants receive study intervention (selumetinib or placebo) for up to twelve 28-day cycles. Treatment after completion of 12 cycles of study intervention was open-label: participants randomized to the selumetinib group continued to receive selumetinib and participants randomized to the placebo group (referred to as the placebo/selumetinib group) were crossed over to selumetinib treatment during the Open-label Period.
Study status; type of report	Completed[b]; interim and primary CSR and an addendum	Ongoing at time of initial submission; primary CSR

[a] The participants were enrolled and not randomized.

[b] Final CSR available; however, some participants remain on study treatment within PTAP.

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

The recommended dose of selumetinib is 25 mg/m2 individualised based on body surface area (BSA) and taken orally twice daily (BID). Dosing is rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg for BSA ≥ 1.9 m2). Selumetinib is not recommended in patients with a BSA < 0.55 m2. Two strengths of hard capsules, 10 and 25 mg are available.

The pharmacokinetic (PK) properties of selumetinib were sufficiently characterized in the initial MAA.

In the context of this type II variation extension of indication, the applicant seeks an extension of the indication to include treatment of iPN adult patients with NF1 based on the results of a Phase 3 pivotal study (**KOMET**, Study **D134BC00001**). This application is also supported by studies for which the CSR had been submitted previously (Study SPRINT, initial MAA, Study 15 II-13, Study 11/13/15-PAM46).

New PK data in adult patients has been provided, and updates of a population pharmacokinetic model (PPK) and exposure-response analyses (ER) were performed.

2.4.2. Pharmacokinetics

Study D134BC0001 (KOMET)

Bioanalysis

In study **D134BC00001**, selumetinib and its active metabolite N-desmethyl selumetinib were quantified in human plasma using the validated ANAHPP HPLC LC-MS/MS method used previously as part of the initial MAA and subsequent type II or PAM46 variation. Specifically for the **KOMET** study, two re-validation were carried out depending on the origin of the sample.

Briefly, calibration, QC and clinical samples (50 µL) were spiked with [$^{13}C_6$] selumetinib and [$^{13}C_6$] N-desmethyl selumetinib as internal standards and using K2-EDTA as anticoagulant. The lower and upper limits of quantification of the method are 2.0 ng/mL and 2000 ng/mL, for selumetinib and 2.00 ng/mL and 500 ng/mL for N-desmethyl selumetinib. For non-Chinese and Chinese samples performance of the methods were cross-validated for both analytes.

Based on the clinical bioanalysis report, approximately 684 PK samples were received from 14 Feb 2022 to 23 Aug 2023 frozen with dry ice and stored at -10°C to -30°C. The total duration of sample storage was 794 days (from first sample collection on 28 Dec 2021 to the last sample analysed on 1st March 2024).

A total of 332 samples were analysed between 15 Jan 2023 to 1st March 2024. 5/5 runs meet the acceptance criteria for selumetinib, however 5/11 for N-desmethyl selumetinib. From the clinical bioanalysis report, from 20 Sept 2023 (Run 4) to 14 Dec 2023 (Run 11), N-desmethyl selumetinib samples from Run 5 were re-extracted 6 times before results were considered acceptable (Run 13, 08 Jan 2024).

No ISR (include sample reanalysis) were performed specifically for study D134BC00001.

Design

This was an ongoing Phase 3, randomized, double-blind, parallel-group, multicentre international study to evaluate safety, efficacy and PK of selumetinib administered orally compared to placebo in adult participants iNP with NF1. The study consisted of a screening period of 28 days, a randomized period (12 cycles) followed by an open-label period. The study will end when the last treated participants has had the opportunity to complete 24 cycles of study intervention.

Approximately 184 subjects were enrolled and 145 were randomized.

At Cycle 1 Day 1, patients received multiple doses of selumetinib 25 mg/m^2 BID (Dose capped at 50 mg for BSA over 1.9) on a continuous schedule (28 days per cycle) for 12 cycles. PK sampling was performed at Cycle 1 Day 8.

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

Results

Study D134BC00001

A total of 64 patients who received selumetinib were included in the PK analysis set.

Selumetinib

Geometric mean selumetinib plasma concentration-time profiles following multiple oral administration of 25 mg/m^2 BID selumetinib at C1D8 are shown in Figure 1 and associated PK parameter estimates in Table 2.

Figure 1: Geometric mean (geometric SD) plasma concentration of selumetinib vs time-Multiple dose C1D8

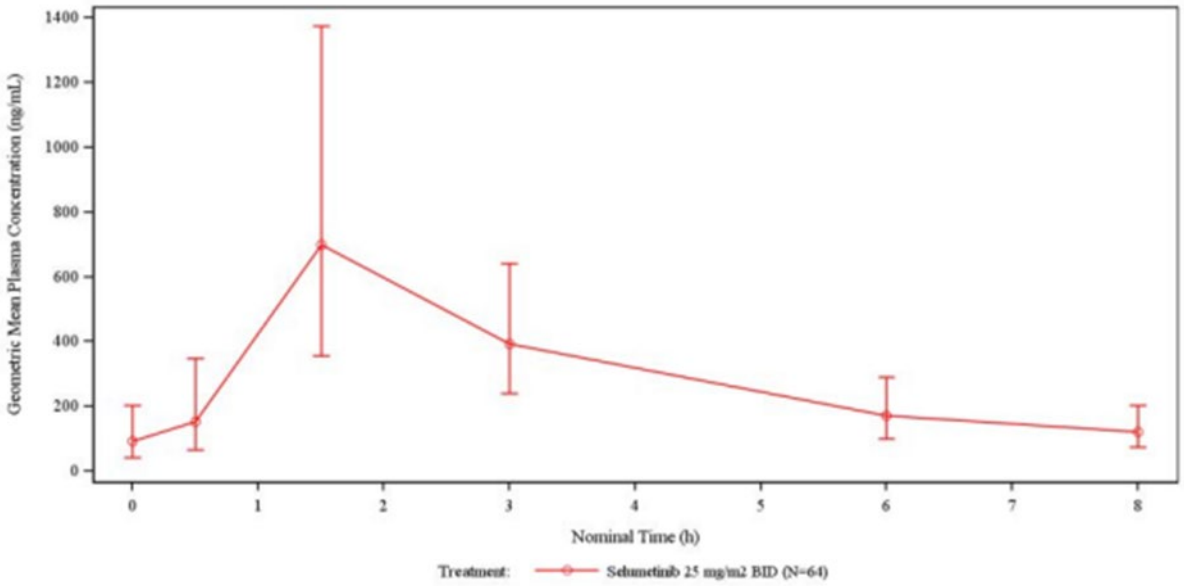


Table 2: Summary of PK parameters of selumetinib, Multiple dose C1D8

Parameter (Units)	Statistic	Selumetinib (N = 64)
C_{max} (ng/mL)	Gmean (gCV%) Min – max [n]	788.8 (46.88%) 225 – 2630 [64]
t_{max} (h)	Median Min – max [n]	1.50 0.50 – 5.97 [64]
$AUC_{(0-6)}$ (h × ng/mL)	Gmean (gCV%) Min – max [n]	2224 (41.56%) 852 – 5580 [63]
$AUC_{(0-8)}$ (h× ng/mL)	Gmean (gCV%) Min – max [n]	2526 (41.66%) 971 – 6280 [63]
$AUC_{(0-12)}$ (h × ng/mL)	Gmean (gCV%) Min – max [n]	2986 (42.65%) 1180 – 7820 [63]
AUC_{last} (h × ng/mL)	Gmean (gCV%) Min – max [n]	2518 (41.56%) 969 – 6270 [63]
t_{last} (h)	Median Min – max [n]	8.00 7.75 – 8.17 [64]
CL/F (L/h)	Gmean (gCV%) Min – max [n]	14.13 (46.11%) 5.12 – 38.0 [63]
Vss/F (L)	Gmean (gCV%) Min – max [n]	126.1 (87.04%) 40.0 – 3710 [61]

Following multiple oral doses of selumetinib 25 mg/m^2 BID in adult patients, absorption of selumetinib was generally rapid with a median Tmax of 1.5h. For selumetinib, geometric mean Cmax was 789 ng/mL, AUC0-12h 2986 ng.h/mL.

N-desmethyl selumetinib

Geometric mean N-desmethyl selumetinib plasma concentration-time profiles following multiple oral administration of 25 mg/m2 BID selumetinib at C1D8 are shown in Figure 2 and associated PK parameter estimates in Table 3.

Figure 2: Geometric mean (geometric SD) plasma concentration of N-desmethyl selumetinib vs time- Multiple doses of selumetinib C1D8

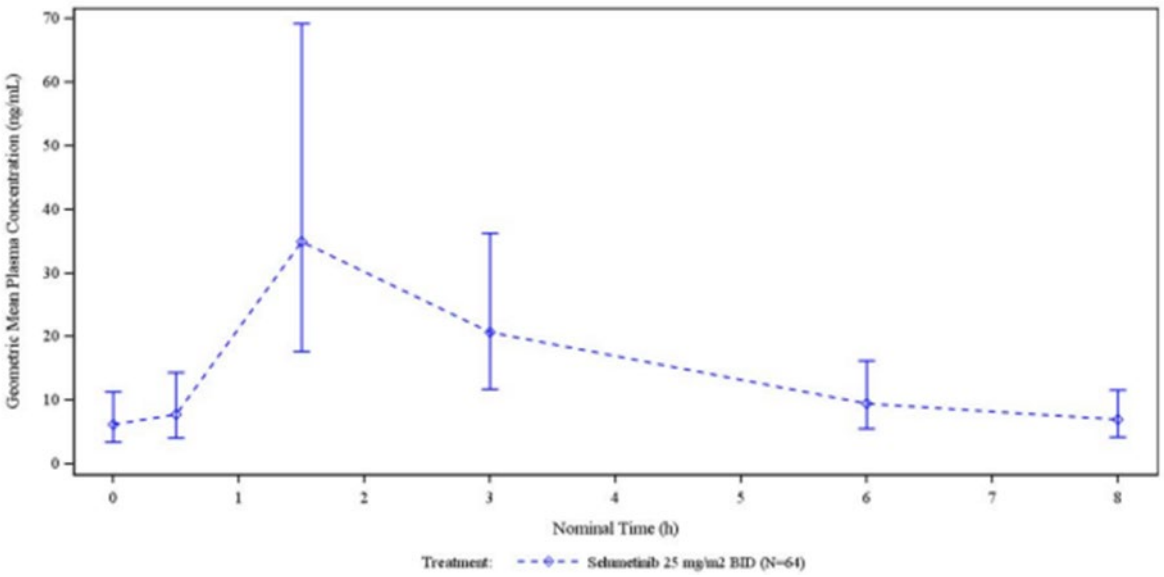


Table 3: Summary of PK parameters of N-desmethyl selumetinib, Multiple dose selumetinib C1D8

Parameter (Units)	Statistic	N-desmethyl Selumetinib (N = 64)
C_{max} (ng/mL)	Gmean (gCV%) Min – max [n]	39.47 (54.68%) 14.1 – 98.7 [64]
t_{max} (h)	Median Min – max [n]	1.50 1.38 – 5.97 [64]
$AUC_{(0-6)}$ (h × ng/mL)	Gmean (gCV%) Min – max [n]	114.3 (49.48%) 34.5 – 266 [63]
$AUC_{(0-8)}$ (h × ng/mL)	Gmean (gCV%) Min – max [n]	131.3 (48.82%) 39.3 – 302 [63]
$AUC_{(0-12)}$ (h × ng/mL)	Gmean (gCV%) Min – max [n]	159.3 (49.15%) 45.5– 381 [62]
AUC_{last} (h × ng/mL)	Gmean (gCV%) Min – max [n]	130.9 (48.85%) 38.8 – 301 [63]
t_{last} (h)	Median Min – max [n]	8.00 7.75 – 8.17 [64]
MPC_{max}	Gmean (gCV%) Min – max [n]	0.05004 (45.02%) 0.0180 – 0.119 [64]
MPAUC	Gmean (gCV%) Min – max [n]	0.05196 (45.02%) 0.0182 – 0.125 [63]

Following multiple oral doses of selumetinib 25 mg/m^2 BID in adult patients, N-desmethyl selumetinib reached Tmax by 1.5h. For N-desmethyl selumetinib, geometric mean C_{max} was 39 ng/mL, AUC0-12h 159 ng.h/mL.

The exposure to the active metabolite N-desmethyl selumetinib was approximately 5% of the parent selumetinib exposure based upon both MPC_{max} and MPAUC.

Population Pharmacokinetic analysis

Methods

PK dataset

As part of the type II variation EMEA/H/C/005244/II/0013 a PPK model was developed and was considered to fit for purpose (PPK 1).

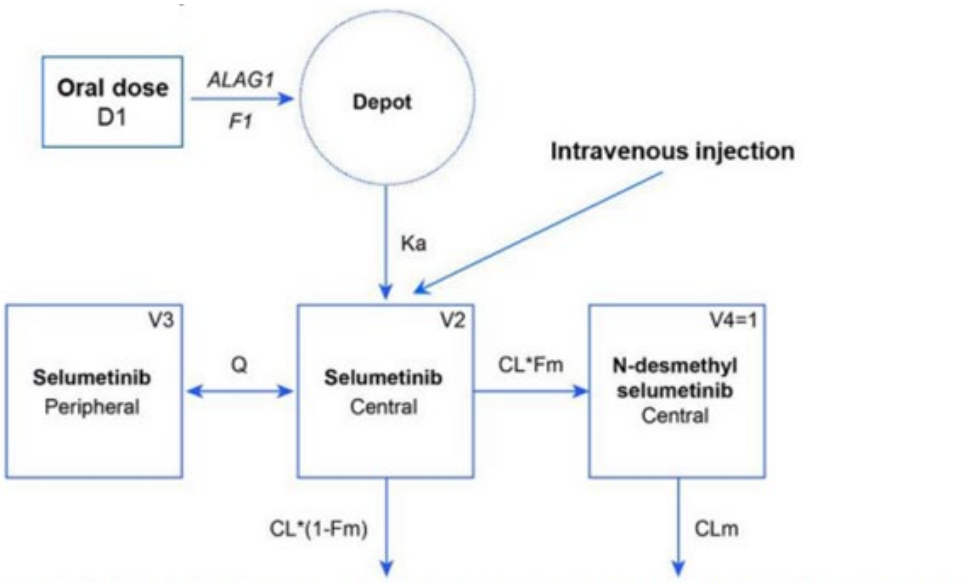
The PK dataset encompasses 15 clinical studies, 10 Phase 1 in HV (Studies **66**, **69**, **71**, **78**, **80**, **81**, **82**, **83**, **85** and **86**), 2 Phase 1 in adult patients (Studies **5** and **20**), 1 Phase 1/2 in children patients (**SPRINT**) and two food effect studies (Studies **15** and **89**).

In this application the previous PPK2 model was updated with additional PK data from the **KOMET** study (cut-off 05/08/24), for a total of 19 studies (PPK3).

Methods

The PK of selumetinib was previously described using a two-compartment model with sequential zero- and first-order delayed absorption and first-order elimination (PPK1). A one-compartment model was used to characterize the metabolite (N-desmethyl selumetinib) plasma concentrations over time, simultaneously with the parent. The conversion of selumetinib to its N-desmethyl metabolite was assumed to be irreversible. The PK structure is presented in Figure 3.

Figure 3: **Schematic representation of Compartment models for selumetinib and N-desmethyl selumetinib**



ALAG1 = selumetinib absorption lag time; CL = selumetinib clearance; CLm = N-desmethyl selumetinib clearance; D1 = Duration of zero-order selumetinib absorption; F1 = bioavailability; Fm = fraction metabolized; Ka = First-order selumetinib absorption rate constant; Q = inter-compartmental selumetinib clearance; V2 = selumetinib volume of distribution of central compartment; V3 = selumetinib volume of distribution of peripheral compartment; V4 = N-desmethyl selumetinib volume of distribution of central compartment.

Based on a recent analysis (PPK2), the PPK model included the following covariates:

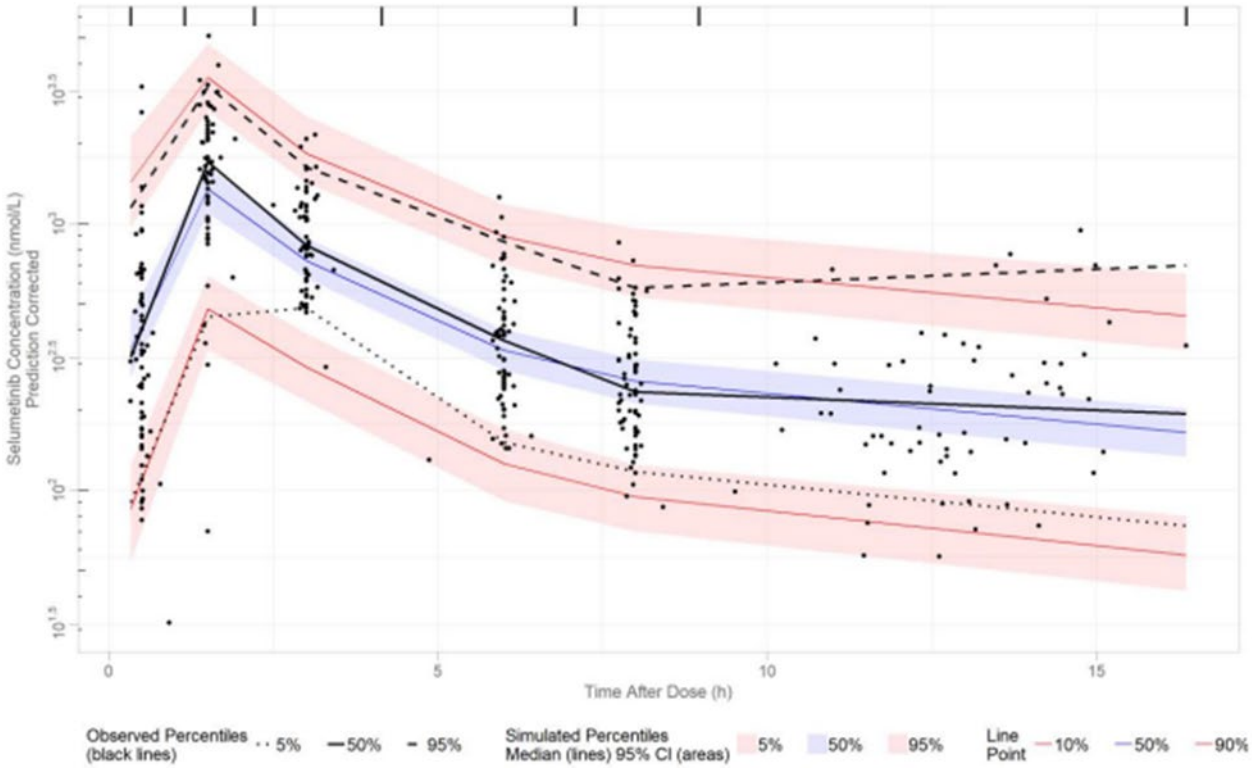
- Formulation (Capsule vs Granule) and healthy status (Healthy vs patients) on Ka

- Effect of meal: Drug administration without regard to food on F1 and D1 (only applicable for Cohort 2 in the SPRINKLE study)
- Baseline albumin on Fm.

Overall a similar methodology as already described in EMEA/H/C/005244/II/0013 was applied when adding in PPK2 the PK data from **KOMET**. Similar GOF plots were computed, model performance was evaluated using pcVPC and descriptive statistics were calculated by simulation for the **KOMET** study.

To note, PPK2 was already able to describe the PK data from the KOMET when these PK data were used as an external validation dataset for PPK2 (Figure 4).

Figure 4: **External validation for selumetinib - KOMET**



Results

PPK3 consisted of 657 subjects who received at least one dose of selumetinib and provided at least one post-dose measurable concentrations of selumetinib and N-desmethyl selumetinib. Adult patients from the KOMET study accounted for 66 subjects.

A total of 10847 and 9029 observations for selumetinib and N-desmethyl selumetinib were available. BQL accounted for 5.8% and 14.6% for selumetinib and N-desmethyl-S respectively and were excluded (Table 4).

Table 4: **Numbers of subjects and observations included in the analysis**

Number of Subjects	**657**
Number of Samples Available in the Dataset	
Selumetinib	11521
N-desmethyl selumetinib	10586
Radioactive [^{14}C] compound	217
Number of Samples Excluded from the Analysis – Missing Dose	
Selumetinib	1
N-desmethyl selumetinib	1
Radioactive [^{14}C] compound	0
Number of Samples Excluded from the Analysis – BLQ Samples	
Selumetinib	669
N-desmethyl selumetinib	1552
Radioactive [^{14}C] compound	0
Number of Hemolyzed Samples – Included in the Analysis	
Selumetinib	51
N-desmethyl selumetinib	50
Radioactive [^{14}C] compound	0
Number of Samples Excluded from the Analysis - Overall	
Selumetinib	674
N-desmethyl selumetinib	1557
Radioactive [^{14}C] compound	0
Final Number of Samples Used in Analysis (% of overall samples included)	
Selumetinib	10847
N-desmethyl selumetinib	9029
Radioactive [^{14}C] compound	217

Abbreviations: ^{14}C = Carbon 14.

Summary of baseline covariates are presented in Table 5. The median age (min-max) was 29.6 years (1-79), median BW 64.6 kg (8.75-123). Male subjects accounted for 76.6%, Caucasian for 55.7% and Asian for 22.4%. Subjects from the **KOMET** study has a median age of 32 (18-60) years, and a median BW of 66.4 (40-114) kg.

Table 5: Baseline covariates (Overall population)

Demographic	≥1 to <3 years (N=13)	≥3 to <7 years (N=43)	≥7 to <18 years (N=98)	≥18 years (N=503)	Overall (N=657)
Age (year)					
Mean (SD)	1.46 (0.519)	4.86 (1.18)	12.6 (3.05)	35.7 (14.1)	29.6 (16.8)
Median [Min, Max]	1.00 [1.00, 2.00]	5.00 [3.00, 6.90]	13.0 [7.00, 17.9]	32.0 [18.0, 79.0]	27.0 [1.00, 79.0]
Percentile [5th, 95th]	[1.00, 2.00]	[3.00, 6.40]	[7.37, 17.0]	[20.0, 64.0]	[5.00, 63.0]
Sex					
Female	6 (46.2%)	20 (46.5%)	45 (45.9%)	83 (16.5%)	154 (23.4%)
Male	7 (53.8%)	23 (53.5%)	53 (54.1%)	420 (83.5%)	503 (76.6%)
Race					
White	10 (76.9%)	28 (65.1%)	62 (63.3%)	266 (52.9%)	366 (55.7%)
Black	0 (0%)	1 (2.3%)	5 (5.1%)	116 (23.1%)	122 (18.6%)
Asian-Chinese	0 (0%)	2 (4.7%)	14 (14.3%)	33 (6.6%)	49 (7.5%)
Asian-Japanese	1 (7.7%)	3 (7.0%)	11 (11.2%)	34 (6.8%)	49 (7.5%)
Asian-Indian	0 (0%)	0 (0%)	0 (0%)	10 (2.0%)	10 (1.5%)
Asian-Other	0 (0%)	2 (4.7%)	3 (3.1%)	34 (6.8%)	39 (5.9%)
Any others	1 (7.7%)	3 (7.0%)	0 (0%)	7 (1.4%)	11 (1.7%)
Missing/Not reported	1 (7.7%)	4 (9.3%)	3 (3.1%)	3 (0.6%)	11 (1.7%)
Body Weight (kg)					
Mean (SD)	11.8 (1.39)	19.0 (3.94)	42.9 (17.3)	74.0 (13.4)	64.6 (22.6)
Median [Min, Max]	12.0 [8.75, 14.3]	18.4 [12.1, 32.5]	41.8 [16.8, 88.7]	74.6 [32.0, 123]	69.6 [8.75, 123]
Percentile [5th, 95th]	[9.50, 13.6]	[14.4, 24.8]	[21.0, 74.1]	[52.0, 94.1]	[17.9, 92.1]
BSA (m^2)					
Mean (SD)	0.522 (0.0509)	0.745 (0.0966)	1.32 (0.330)	1.87 (0.200)	1.69 (0.422)
Median [Min, Max]	0.530 [0.420, 0.620]	0.751 [0.540, 0.970]	1.34 [0.690, 2.02]	1.89 [1.07, 2.40]	1.82 [0.420, 2.40]
Percentile [5th, 95th]	[0.432, 0.584]	[0.630, 0.883]	[0.835, 1.88]	[1.50, 2.17]	[0.710, 2.15]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.2%)
Subject type					
NF1 Patient	13 (100%)	43 (100%)	98 (100%)	169 (33.6%)	323 (49.2%)
Healthy	0 (0%)	0 (0%)	0 (0%)	334 (66.4%)	334 (50.8%)

Demographic	Pediatric (≥1 to <3 years) (N=13)	Pediatric (≥3 to <7 years) (N=43)	Pediatric (≥7 to <18 years) (N=98)	Adult (≥18 years) (N=503)	Overall (N=657)
Albumin (g/L)					
Mean (SD)	42.8 (4.92)	42.1 (2.63)	44.1 (3.72)	42.5 (5.25)	42.7 (4.94)
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]	[37.9, 49.2]	[32.0, 49.0]	[34.0, 49.0]
Missing	2 (15.4%)	1 (2.3%)	0 (0%)	1 (0.2%)	4 (0.6%)
ALP (U/L)					
Mean (SD)	186 (41.9)	176 (39.5)	190 (151)	89.3 (100)	112 (113)
Median [Min, Max]	190 [119, 281]	172 [124, 280]	148 [51.0, 881]	68.0 [13.0, 1330]	77.0 [13.0, 1330]
Percentile [5th, 95th]	[123, 244]	[127, 244]	[74.7, 569]	[43.0, 194]	[44.0, 254]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.2%)
ALT (µkat/L)					
Mean (SD)	0.324 (0.144)	0.298 (0.155)	0.249 (0.109)	0.404 (0.191)	0.372 (0.187)
Median [Min, Max]	0.283 [0.100, 0.600]	0.283 [0.100, 1.00]	0.233 [0.0830, 0.767]	0.367 [0.100, 1.23]	0.333 [0.0830, 1.23]
Percentile [5th, 95th]	[0.150, 0.550]	[0.135, 0.545]	[0.132, 0.433]	[0.166, 0.746]	[0.150, 0.704]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.2%)
AST (µkat/L)					
Mean (SD)	0.555 (0.0870)	0.492 (0.243)	0.331 (0.164)	0.395 (0.176)	0.395 (0.183)
Median [Min, Max]	0.567 [0.383, 0.700]	0.433 [0.267, 1.90]	0.300 [0.117, 1.48]	0.367 [0.133, 1.84]	0.367 [0.117, 1.90]
Percentile [5th, 95th]	[0.433, 0.670]	[0.335, 0.710]	[0.187, 0.591]	[0.217, 0.697]	[0.217, 0.687]
Missing	0 (0%)	0 (0%)	0 (0%)	2 (0.4%)	2 (0.3%)
Bilirubin (mg/dL)					
Mean (SD)	0.330 (0.146)	0.431 (0.188)	0.551 (0.364)	0.652 (0.301)	0.616 (0.312)
Median [Min, Max]	0.300 [0.160, 0.600]	0.410 [0.200, 1.13]	0.511 [0.205, 3.15]	0.600 [0.158, 2.87]	0.579 [0.158, 3.15]
Percentile [5th, 95th]	[0.184, 0.600]	[0.200, 0.717]	[0.205, 1.15]	[0.300, 1.20]	[0.270, 1.18]
Missing	0 (0%)	1 (2.3%)	0 (0%)	1 (0.2%)	2 (0.3%)
Serum Creatinine (mg/dL)					
Mean (SD)	0.275 (0.0789)	0.343 (0.0805)	0.497 (0.161)	0.895 (0.186)	0.787 (0.266)
Median [Min, Max]	0.290 [0.150, 0.400]	0.330 [0.200, 0.599]	0.490 [0.200, 0.950]	0.900 [0.407, 1.55]	0.814 [0.150, 1.55]
Percentile [5th, 95th]	[0.156, 0.376]	[0.260, 0.479]	[0.266, 0.752]	[0.599, 1.20]	[0.300, 1.20]
Creatinine Clearance ($mL/min/1.73m^2$)					
Mean (SD)	173 (41.6)	205 (48.2)	194 (56.3)	111 (25.1)	131 (49.3)
Median [Min, Max]	170 [110, 251]	198 [131, 327]	186 [100, 418]	110 [40.0, 192]	119 [40.0, 418]
Percentile [5th, 95th]	[113, 235]	[136, 285]	[127, 281]	[69.1, 156]	[73.6, 233]
Missing	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)	1 (0.2%)

Final PPK model

Table 6provides the final PK parameter estimates of PPK3 and Figure 5 and Figure 6 the associated GOF and pcVPC, respectively for both analytes.

The absorption of selumetinib was described by an oral administration bioavailability (F1) of 63.4%, an absorption lag time of 0.365 h, a duration of absorption (D1) of 0.576 h and a first-order rate constant of absorption (Ka) of 4.29 h -1.

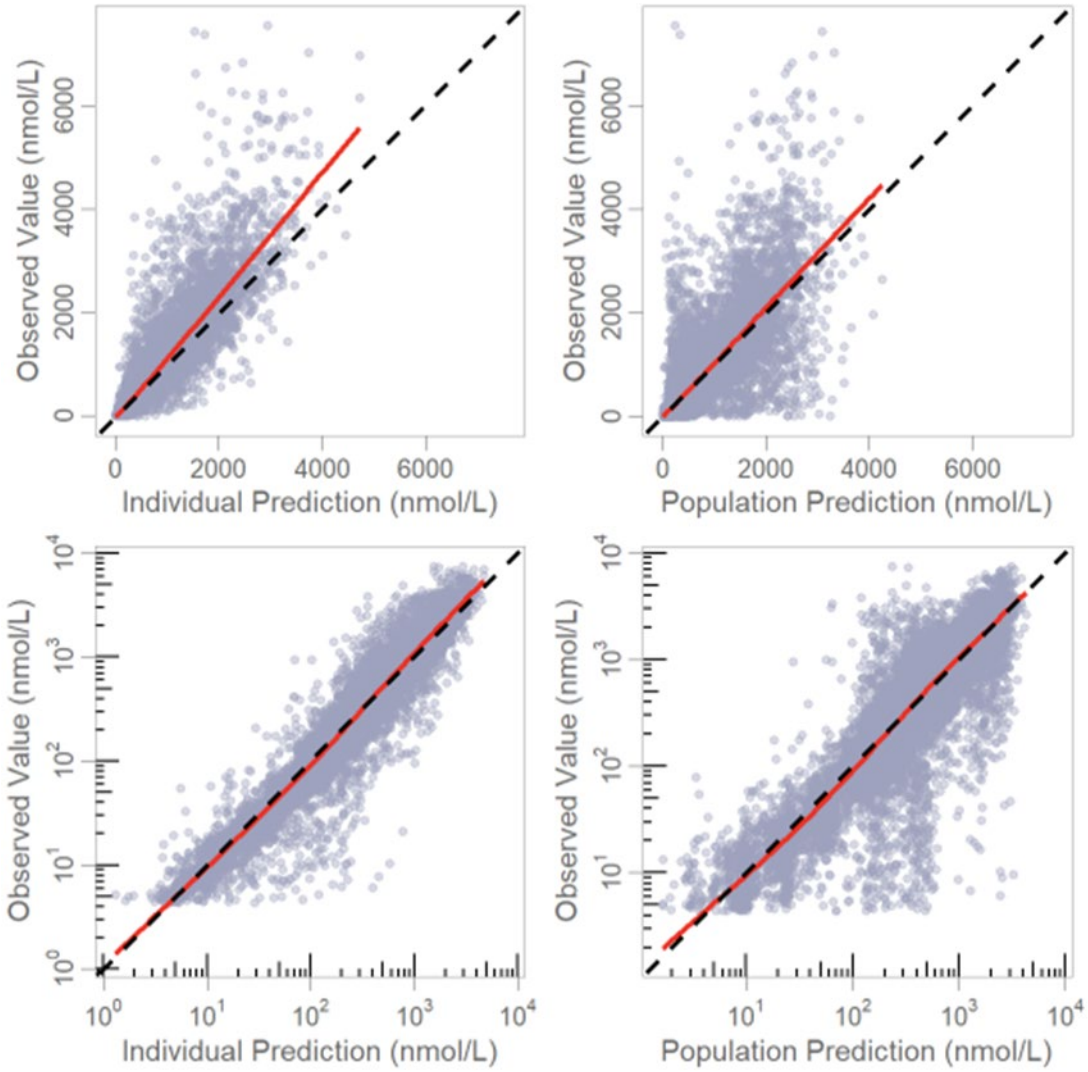
Population estimates of selumetinib CL and V2 were 10.7 L/h and 29.2 L in a typical subject with a BSA of 1.8 m^2. Based on clearance (CL and Q) and volume of distribution (V2 and V3) estimates of the 2-compartment model, the half-life associated with the alpha (t1/2a) and beta (t1/2b) phases were 1.01 and 9.04 h, respectively.

All population PK parameters were robustly estimated with RSE values less than 25%. Parameters were consistent with those derived in the PPK2 model and all covariates previously identified were retained in the model (i.e., formulation and healthy status on Ka, effect of meal on F1 and D1 and baseline albumin on Fm).

Table 6: **final PK parameter estimates (PPK3)**

Parameter	Estimate	RSE%	95% CI	Shrinkage
Selumetinib				
F1 (logit)	0.551	21.0	0.324, 0.778	NA
ALAG1 (h)	0.365	2.12	0.350, 0.380	NA
D1 (h)	0.576	1.59	0.558, 0.594	NA
Ka (1/h)	4.29	12.5	3.24, 5.33	NA
CL (L/h)	10.7	4.36	9.77, 11.6	NA
V2 (L)	29.2	5.28	26.2, 32.2	NA
Q (L/h)	7.37	4.27	6.75, 7.98	NA
V3 (L)	51.4	4.79	46.6, 56.3	NA
N-Desmethyl Selumetinib				
Fm (logit)	-1.83	4.04	-1.98, -1.69	NA
CLm (L/h)	17.9	5.40	16.0, 19.8	NA
Covariate Effects				
Low fat meal on F1	-0.687	5.88	-0.766, -0.608	NA
High fat meal on F1	-0.411	10.1	-0.493, -0.330	NA
Without regard to food on F1*	0.418	36.3	0.121, 0.716	NA
Low fat meal on D1	1.40	1.16	1.37, 1.44	NA
High fat meal on D1	1.21	2.24	1.15, 1.26	NA
Without regard to food on D1*	0.287	39.4	0.0653, 0.508	NA
Low fat meal on Ka^	-0.214	8.18	-0.248, -0.180	NA
High fat meal on Ka^	-2.75	2.14	-2.87, -2.64	NA
Granule on Ka	-2.35	1.36	-2.42, -2.29	NA
Health Status on Ka	1.29	11.0	1.01, 1.57	NA
Age on clearances	-0.0854	24.0	-0.126, -0.0452	NA
BSA on clearances	0.927	6.16	0.815, 1.04	NA
Race (Asian) on CL	-0.120	19.5	-0.166, -0.0740	NA
BSA on V2	1.66	7.06	1.43, 1.89	NA
BSA on V3	0.489	11.2	0.382, 0.597	NA
BSA on Fm	-1.19	5.56	-1.32, -1.06	NA
BALB on Fm	1.08	9.21	0.884, 1.27	NA
Between-Subject Variability[a]				
On $ALAG_1$	0.401	3.20	0.376, 0.426	13.5%
On Ka	1.55	4.33	1.42, 1.69	19.4%
On CL	0.245	3.44	0.228, 0.261	12.3%
On V2	0.411	3.83	0.381, 0.442	24.4%
On V3	0.372	4.44	0.340, 0.405	28.4%
On Fm	0.400	2.86	0.377, 0.422	6.78%
Correlation CL, V2	0.623	6.19	0.547, 0.698	NA
Residual Error				
Selumetinib additive error (log(nmol/L))	0.499	0.360	0.496 – 0.503	NA
N-desmethyl selumetinib additive error (log(nmol/L))	0.397	0.471	0.393 – 0.400	NA
[14C]-selumetinib additive error (log(nmol/L))	0.418	2.59	0.397 – 0.439	NA

Figure 5: **GOF plots of selumetinib and N-desmethyl selumetinib (PPK3)**



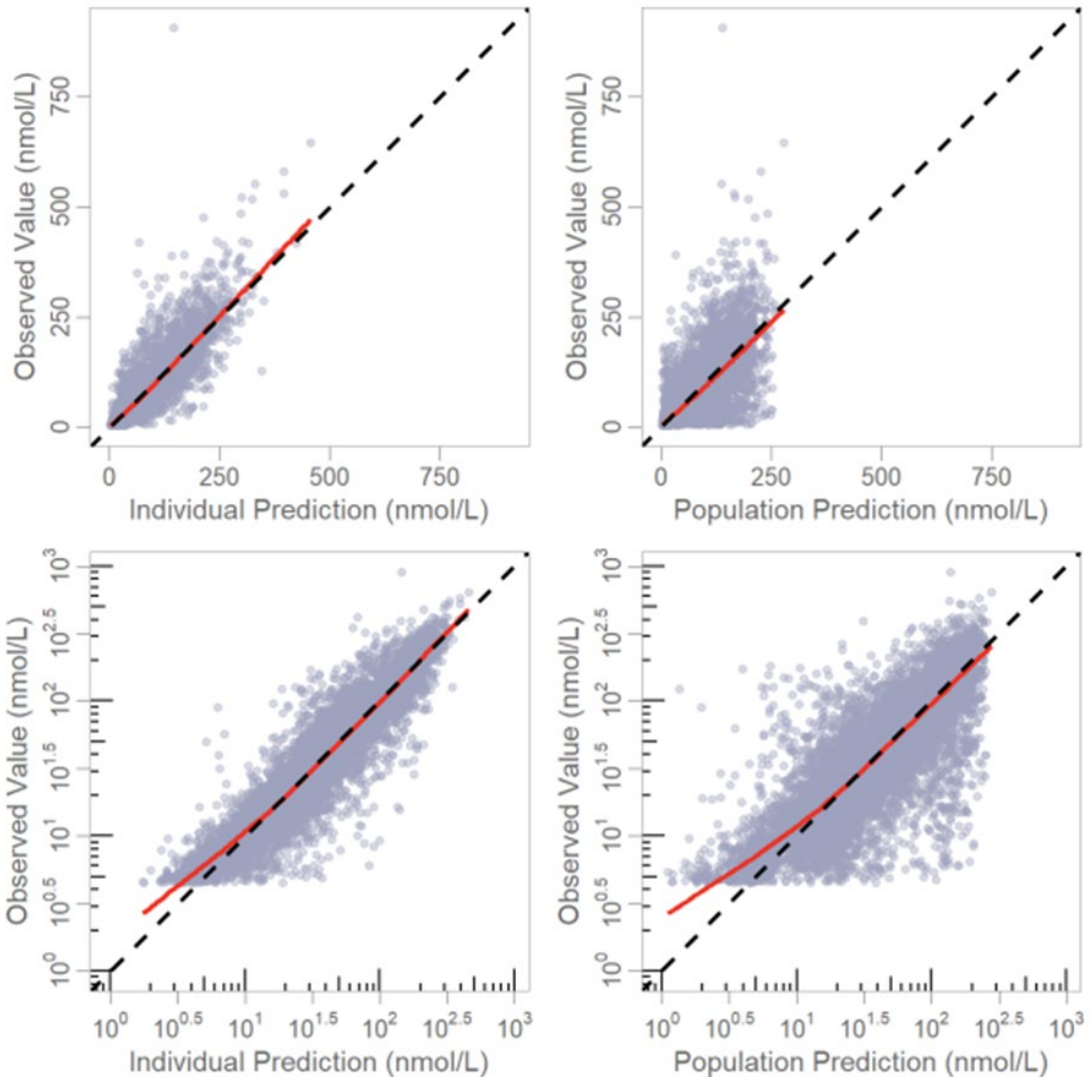
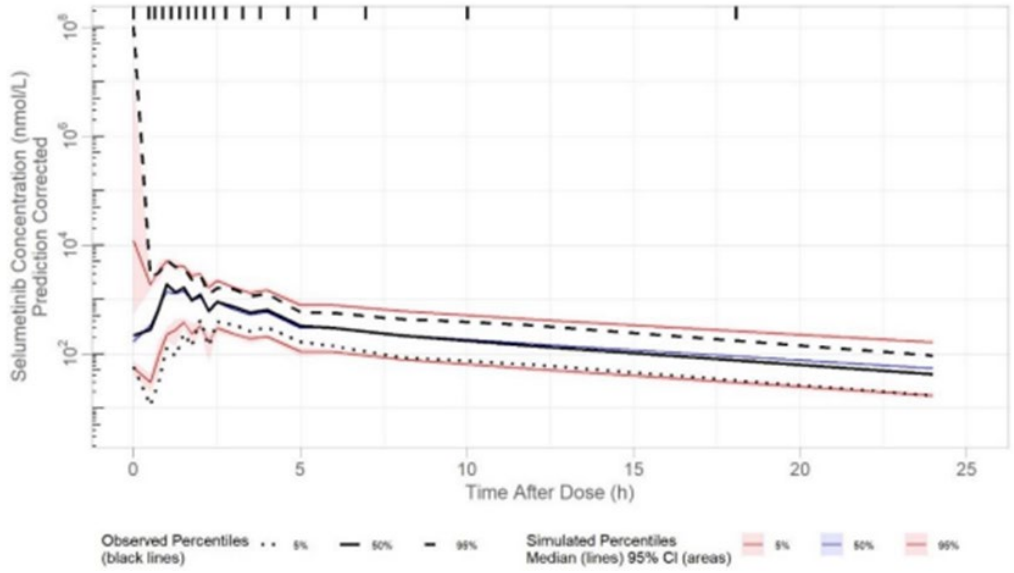
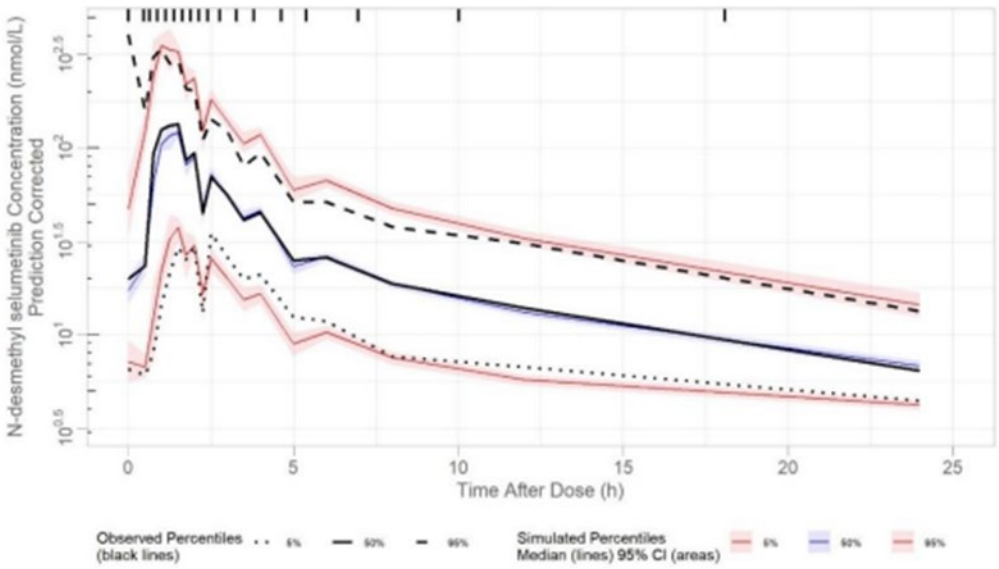


Figure 6: **pcVPC of selumetinib (up) and N desmethyl selumetinib (down) concentrations**





Simulations

Based on the population PK model (PPK3), rich concentration time-profiles of selumetinib and N-desmethyl selumetinib were simulated and AUC (AUC0-6, AUC0-8 and AUC0-12) values at Cycle 1 Day 8 in the **KOMET** study were derived. A comparison of population PK model-derived and NCA-derived AUC values at Cycle 1 Day 8 in KOMET are presented in Table 7. Simulated PK parameters for both analytes at steady-state are presented in Table 8.

Table 7: **Comparison of model-derived and NCA-derived AUC values (KOMET)**

Parameters	Model-Derived (N=66)	NCA-Derived (N=66)
Selumetinib AUC_{0-8} (ng.h/mL)		
Geometric Mean (CV)	2560 (22.0)	2520 (40.9)
Mean (CV)	2620 (22.6)	2720 (41.0)
Median [Min, Max]	2570 [1630, 4650]	2560 [971, 6280]
N-Desmethyl Selumetinib AUC_{0-8} (ng.h/mL)		
Geometric Mean (CV)	152 (35.5)	130 (48.6)
Mean (CV)	161 (32.8)	143 (44.0)
Median [Min, Max]	155 [58.2, 307]	132 [39.3, 302]

Parameters	Model-Derived (N=66)	NCA-Derived (N=66)
Selumetinib AUC_{0-12} (ng.h/mL)		
Geometric Mean (CV)	3380 (25.4)	2970 (42.2)
Mean (CV)	3490 (26.8)	3220 (42.6)
Median [Min, Max]	3400 [1980, 6580]	2990 [1180, 7820]
Missing	0 (0%)	1 (1.5%)
N-Desmethyl Selumetinib AUC_{0-12} (ng.h/mL)		
Geometric Mean (CV)	200 (35.8)	157 (49.4)
Mean (CV)	212 (33.2)	174 (44.1)
Median [Min, Max]	209 [74.0, 466]	169 [45.5, 381]
Missing	0 (0%)	2 (3.0%)

Table 8: **Descriptive statistics of exposure parameters of selumetinib and N-desmethyl selumetinib (Molar and Mass units). KOMET**

Parameters	Overall (N=66)	
	Molar Units	Mass Units
Selumetinib AUC_{ss}		
Geometric Mean (CV)	7380 (25.4)	3380 (25.4)
Mean (CV)	7610 (26.8)	3490 (26.8)
Median [Min, Max]	7430 [4340, 14400]	3400 [1980, 6580]
Percentile [5th, 95th]	[5090, 10900]	[2330, 5000]
Selumetinib $C_{max,ss}$		
Geometric Mean (CV)	1630 (29.5)	745 (29.5)
Mean (CV)	1700 (28.7)	776 (28.7)
Median [Min, Max]	1640 [678, 3220]	749 [310, 1470]
Percentile [5th, 95th]	[1020, 2470]	[468, 1130]
Selumetinib $C_{min,ss}$		
Geometric Mean (CV)	532 (106.0)	243 (106.0)
Mean (CV)	749 (80.1)	343 (80.1)
Median [Min, Max]	530 [112, 2760]	243 [51.2, 1260]
Percentile [5th, 95th]	[134, 1890]	[61.2, 867]
N-Desmethyl Selumetinib AUC_{ss}		
Geometric Mean (CV)	451 (35.8)	200 (35.8)
Mean (CV)	478 (33.2)	212 (33.2)
Median [Min, Max]	471 [167, 1050]	209 [74.0, 466]
Percentile [5th, 95th]	[239, 707]	[106, 314]
N-Desmethyl Selumetinib $C_{max,ss}$		
Geometric Mean (CV)	97.8 (39.6)	43.4 (39.6)
Mean (CV)	105 (36.6)	46.5 (36.6)
Median [Min, Max]	102 [38.5, 193]	45.4 [17.1, 85.6]
Percentile [5th, 95th]	[52.7, 176]	[23.4, 78.2]
N-Desmethyl Selumetinib $C_{min,ss}$		
Geometric Mean (CV)	32.1 (108.0)	14.3 (108.0)
Mean (CV)	46.0 (86.1)	20.4 (86.1)
Median [Min, Max]	29.4 [5.41, 192]	13.1 [2.40, 85.2]
Percentile [5th, 95th]	[7.59, 120]	[3.37, 53.2]

Exposure-Response analysis

Methods

Following PPK3 (see above), derived PK metrics for selumetinib and N-desmethyl selumetinib were computed by simulation (Table 8). The simulated metrics were used to identify relationships between selumetinib exposure and efficacy or safety endpoints.

ER-efficacy

Efficacy endpoints from the **KOMET** study consisted of:

- Best Objective response: Progressive disease (PD), stable disease (SD), non-evaluable (NE), partial response (PR) and confirmed PR (cPR)
- ORR. PD/SD/NE and PR were considered as non-responders and cPR as responders.

Graphical analyses were first performed by deriving boxplots of selumetinib/Ndesmethyl-selumetinib exposure metrics vs BOR/ORR. For ORR, a binomial logistic regression model was applied.

Additional efficacy endpoints were explored as PAINS-pNF and PlexiQoL score change in Cycle 12. Graphical analyses were first performed by deriving boxplots of selumetinib/Ndesmethyl-selumetinib in patients with "No change/worsening" (No change ≤ 2 point decrease to 2 point increase; worsening ≥

2 point increase) vs "Improvement" (≤ 2 point decrease from baseline). Linear regression was performed to assess the relationship between the exposure metrics of selumetinib and percent change from baseline in PAINS-pNF and PlexiQoL.

ER-safety

Safety endpoints explored were adverse events of special interest (AESI) graded as 0 (no event), 1 (Mild), 2 (Moderate), 3 (Severe), 4 (Life-threatening) and 5 (Death). Frequency counts were derived. AESI were skin toxicities, nail disorder, oral mucositis, haematology toxicities, gastro-intestinal toxicities, Cardiac, Muscular, Ocular, Hepatotoxicity…

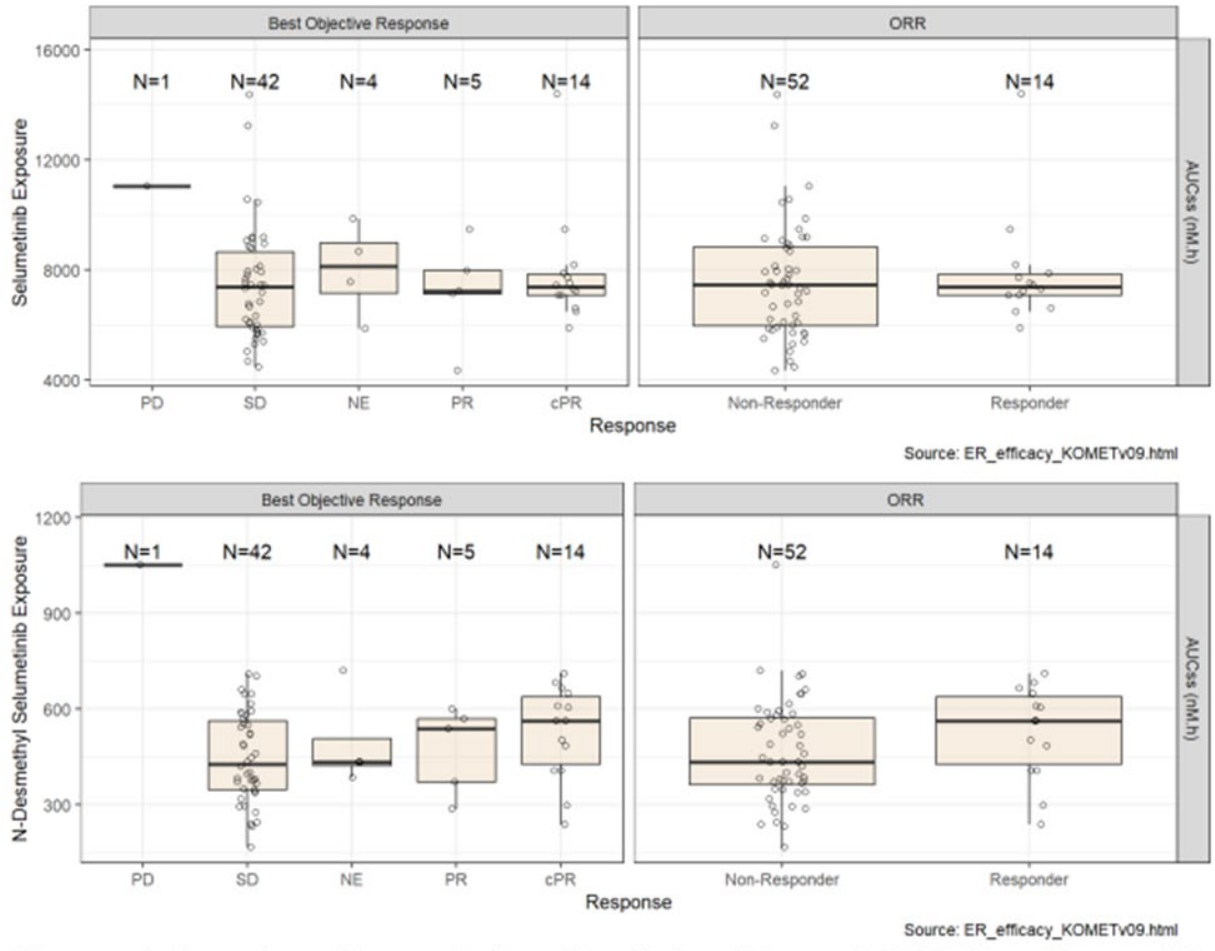
Graphical exploration was solely performed and no regression analysis.

Results

ER-efficacy

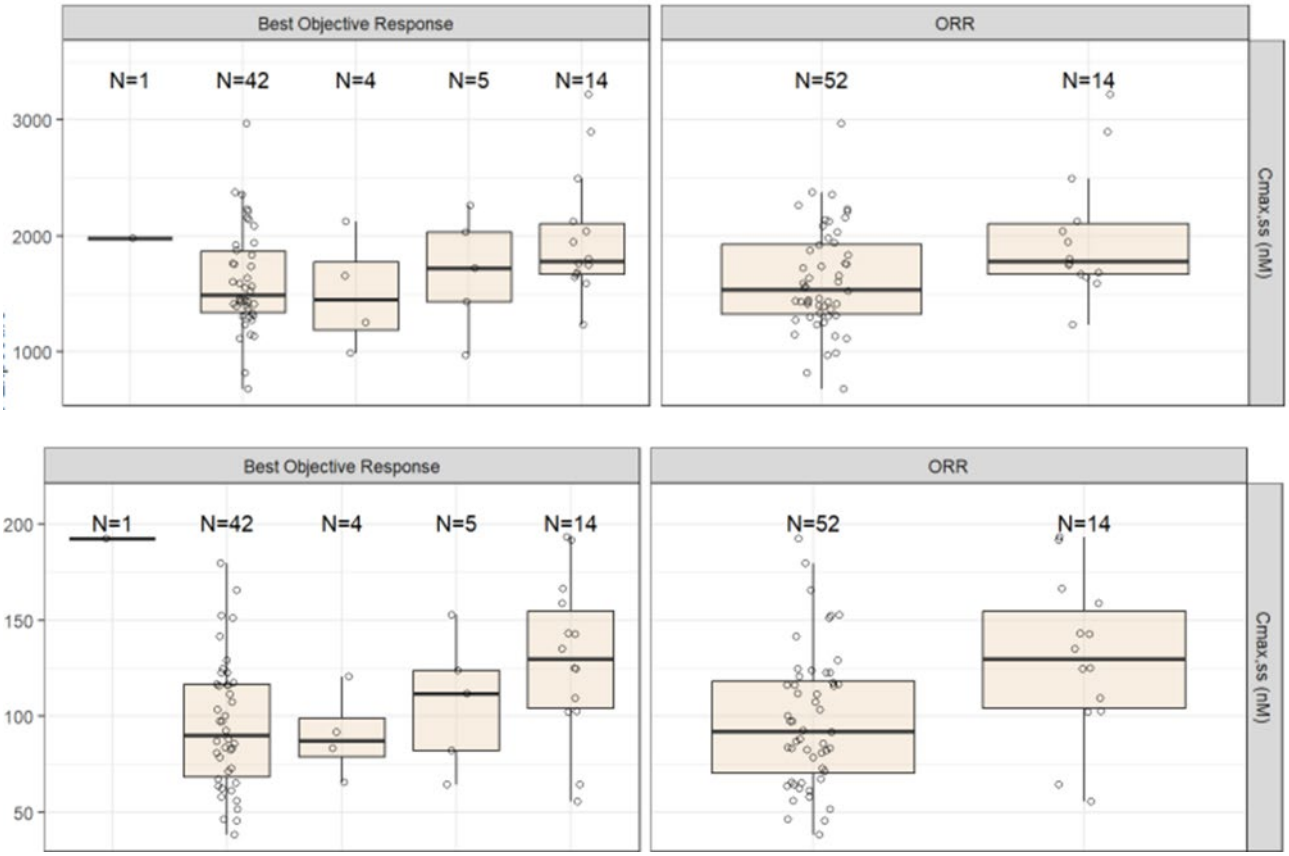
BOR and ORR data from 66 subjects from the KOMET study were available. 14 subjects were considered as responders. Box-plots of AUCss for selumetinib and N-desmethyl selumetinib are presented in Figure 7 and for C_{maxss} in Figure 8. Non-responders and responders for ORR presented overlapping AUCss of selumetinib.

Figure 7: **Exploratory ER analysis, AUCss of selumetinib and N desmethyl selumetinib vs ORR and BOR**



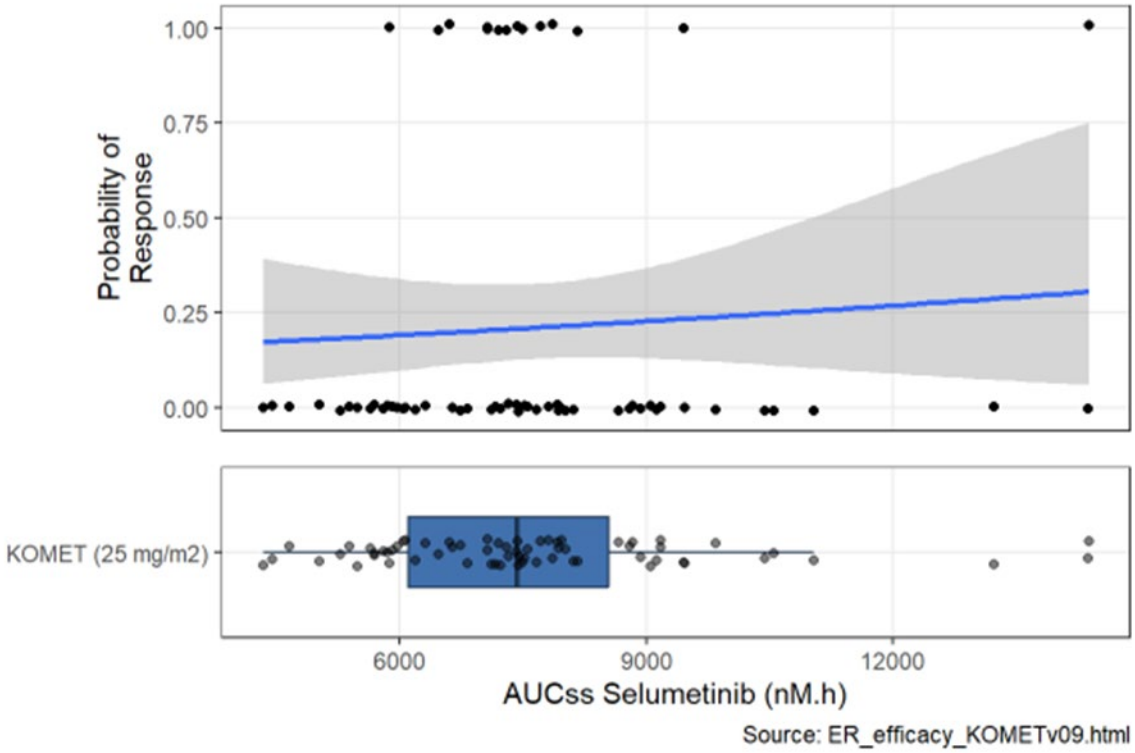
AUC_{ss} = area under the at steady state; PD = progressive disease; SD = stable disease; NE = non-evaluable (NE), PR = partial response, ORR = objective response rate.

Figure 8: **Exploratory ER analysis, Cmaxss of selumetinib (up) and N desmethyl selumetinib (down) vs ORR and BOR**



A binomial logistic regression model was developed to assess the relationship between the AUCss of selumetinib and the probability of observing a response in terms of ORR. The probability of observing a response (ORR) as function of selumetinib AUCss is presented in Figure 9.

Figure 9: **Exploratory ER analysis, Logistic regression for the Probability of ORR vs AUCss selumetinib**

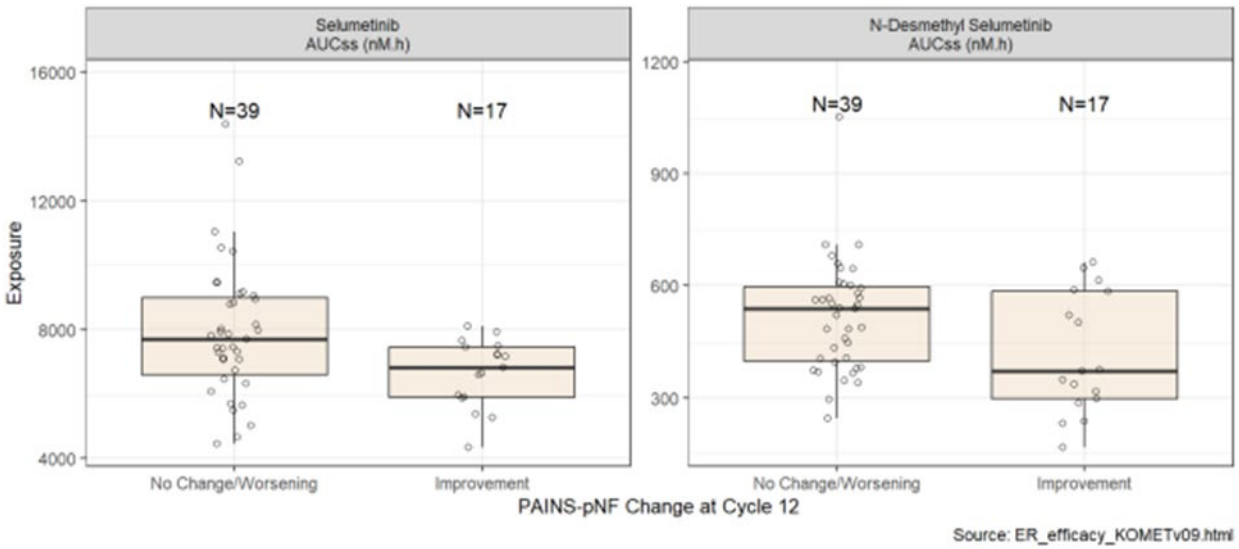


AUC_{ss} = area under the curve at steady state; ORR = objective response rate

The slope of the exposure-response model was not statistically significant (p=0.604), suggesting that lower and higher exposures of selumetinib achieved at clinical doses (i.e., 25 mg/m2 BID) in **KOMET** were associated with similar effects.

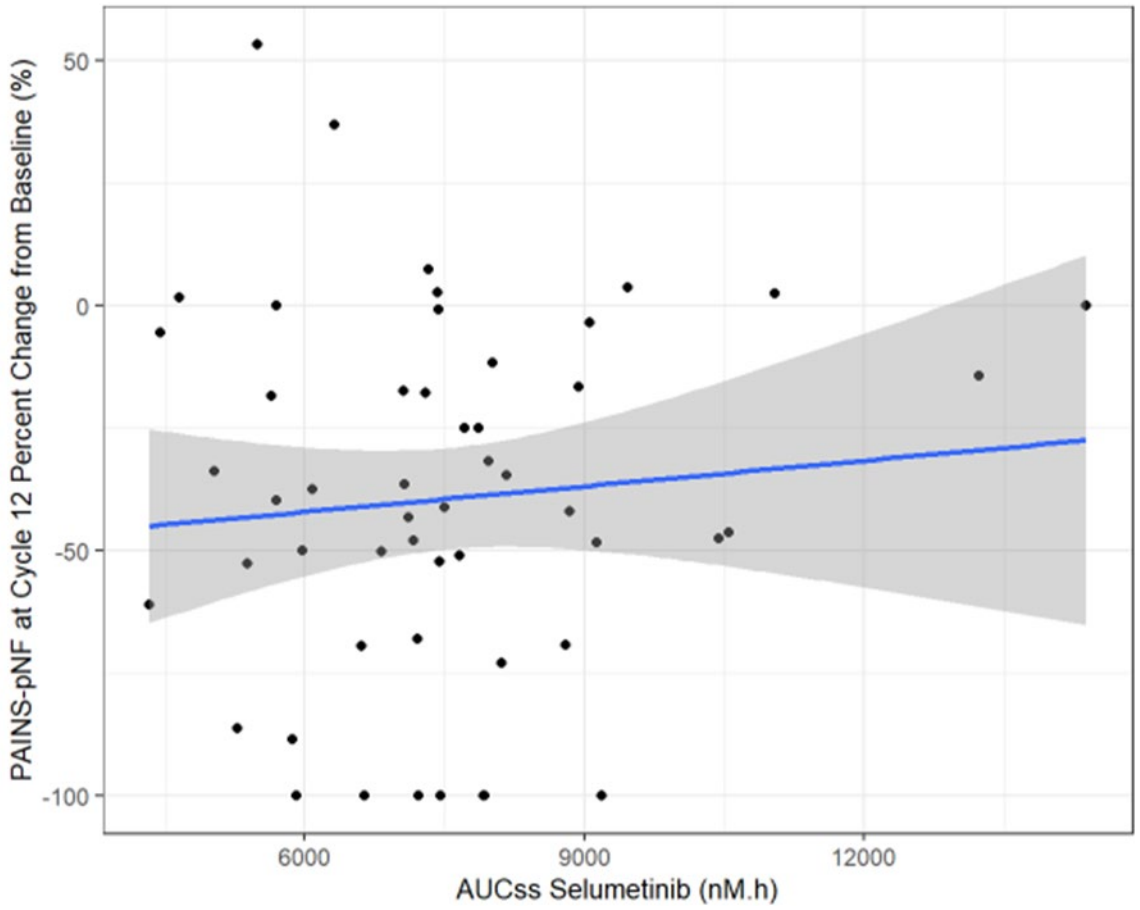
Boxplots of AUCss for selumetinib and N-desmethyl selumetinib in patients with "Worsening/No Change" and "Improvement" in PAINS-pNF scores at Cycle 12 relative to baseline are presented in Figure 10 and the associated regression analysis in Figure 11.

Figure 10: **Exploratory Exposure-Response Analysis – AUCss of Selumetinib and N-Desmethyl Selumetinib in Patients with "Worsening/No Change" and "Improvement" in PAINS-pNF at Cycle 12**



AUC_{ss} = area under the curve at steady state; PAINS-pNF = PAin INtensity Scale for plexiform neurofibroma
Note: Improvement is defined as ≥ 2-point decrease from baseline; No change is defined as <2-point decrease to <2-point increase, from baseline; and Worsening is defined as ≥2-point increase in score from baseline

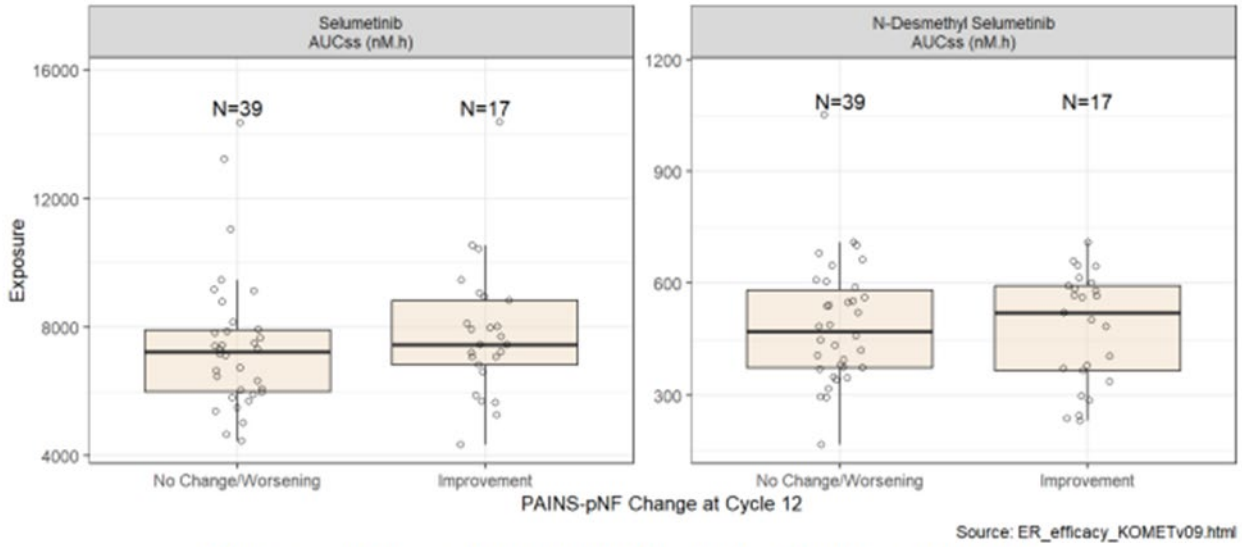
Figure 11: **Exposure-Response Relationship between Selumetinib AUCss and Percent Change from Baseline PAINS-pNF: at Cycle 12**



A statistically significant -52.5% change from baseline in PAINS-pNF score was observed (p=0.0133) for selumetinib treatment (intercept). The slope of the exposure-response model was not statistically significant, suggesting that lower and higher exposures of selumetinib achieved at clinical doses (i.e., 25 mg/m2 BID) in KOMET were associated with similar effects.

Boxplots of AUCss for selumetinib and N-desmethyl selumetinib in patients with "Worsening/No Change" and "Improvement" in PlexiQoL scores at Cycle 12 relative to baseline are presented in Figure 12 and its associated regression analysis in Figure 13.

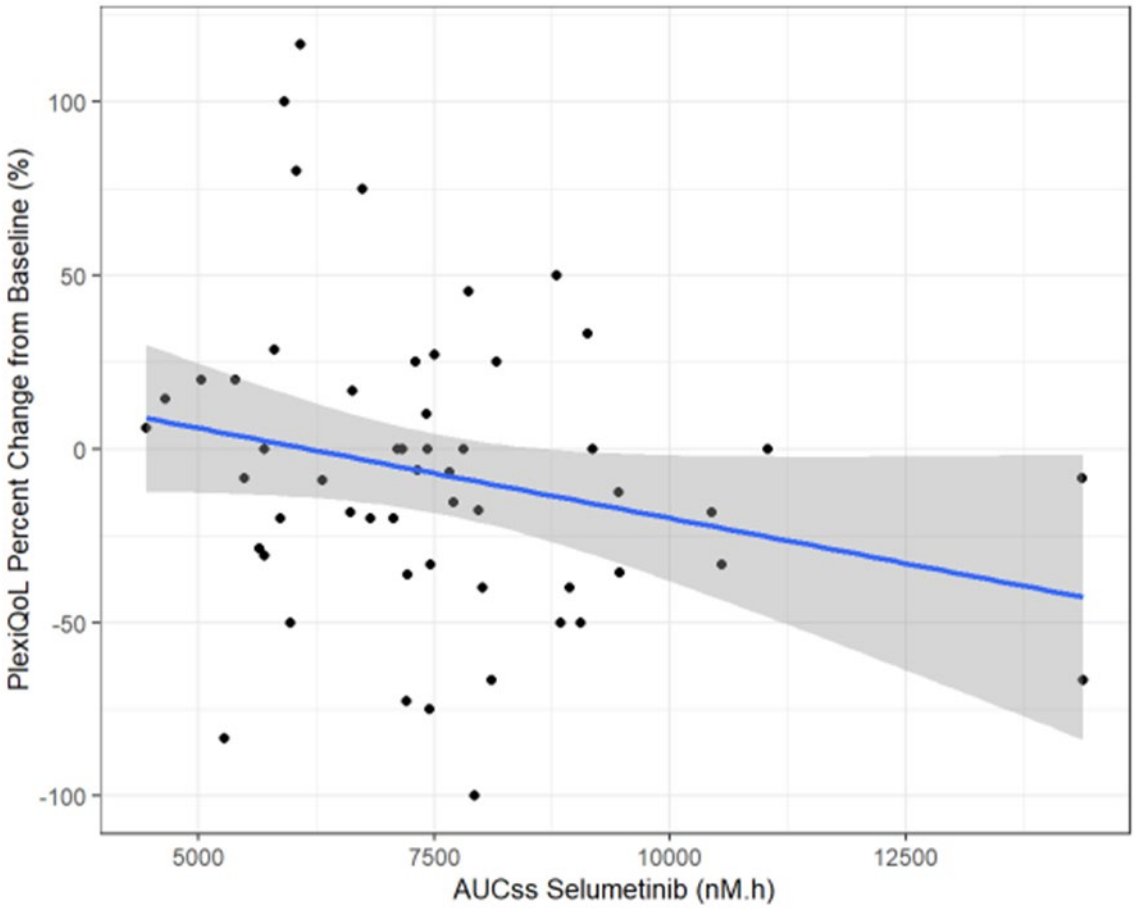
Figure 12: **Exploratory Exposure-Response Analysis – AUCss of Selumetinib and NDesmethyl Selumetinib in Patients with "Worsening/No Change" and "Improvement" in PlexiQoL Scores at Cycle 12**



AUC_{ss} = area under the curve at steady state; PlexiQoL = Plexiform Neurofibroma Quality of Life
Note: Improvement is defined as ≥ 2-point decrease from baseline; No change is defined as <2-point decrease to <2-point increase, from baseline; and Worsening is defined as ≥2-point increase in score from baseline

As part of the above analysis, one patient was considered a statistical outlier and therefore removed from the analysis. An apparent trend was observed for the exposure-response relationship of PlexiQoL (p-value = 0.0772), whereby higher exposures of selumetinib achieved at clinical doses (i.e., 25 mg/m2 BID) in KOMET were associated with a trend for a higher degree of reduction in PlexiQoL.

Figure 13: **Exposure-Response Relationship Between Selumetinib AUCss and Percent Change from Baseline PlexiQoL at Cycle 12**



ER-safety

The number of adverse events by CTC grade including all patients from the KOMET study are presented in Table 9 and the associated results from the binomial regression logistic regression for the probability of each AE are presented in Table 10.

Table 9: Number of AE at each CTC grade in Patients with measurable selumetinib concentrations

Adverse Event	N	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute kidney injury	66	66 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac toxicity	66	46 (69.7%)	14 (21.21%)	4 (6.06%)	2 (3.03%)	0 (0%)	0 (0%)
Chromaturia	66	66 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Constipation	66	58 (87.88%)	8 (12.12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dermatitis and Eczema	66	65 (98.48%)	0 (0%)	1 (1.52%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	66	37 (56.06%)	27 (40.91%)	2 (3.03%)	0 (0%)	0 (0%)	0 (0%)
Erythropenic events	66	61 (92.42%)	3 (4.55%)	2 (3.03%)	0 (0%)	0 (0%)	0 (0%)
Hepatotoxicity	66	53 (80.3%)	10 (15.15%)	2 (3.03%)	1 (1.52%)	0 (0%)	0 (0%)
Hypocalcaemia	66	66 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Leukopenic events	66	66 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Lymphopenic events	66	64 (96.97%)	2 (3.03%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Muscular toxicity	66	33 (50%)	25 (37.88%)	5 (7.58%)	2 (3.03%)	1 (1.52%)	0 (0%)
Nail disorders	66	52 (78.79%)	8 (12.12%)	5 (7.58%)	1 (1.52%)	0 (0%)	0 (0%)
Nausea	66	50 (75.76%)	12 (18.18%)	4 (6.06%)	0 (0%)	0 (0%)	0 (0%)
Neutropenic events	66	64 (96.97%)	2 (3.03%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ocular toxicity	66	62 (93.94%)	4 (6.06%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Oral mucositis	66	53 (80.3%)	10 (15.15%)	3 (4.55%)	0 (0%)	0 (0%)	0 (0%)
Rash acneiform	66	28 (42.42%)	24 (36.36%)	14 (21.21%)	0 (0%)	0 (0%)	0 (0%)
Rash non-acneiform	66	36 (54.55%)	26 (39.39%)	4 (6.06%)	0 (0%)	0 (0%)	0 (0%)
Skin infection	66	60 (90.91%)	5 (7.58%)	1 (1.52%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenic events	66	66 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vomiting	66	48 (72.73%)	17 (25.76%)	1 (1.52%)	0 (0%)	0 (0%)	0 (0%)

Source: ER_Safety_REDUCEKOMET_v04.html

Table 10: Exploratory Exposure-Response Analysis - Statistical Outputs of Logistic Regression for the Probability of Each Adverse Event

Adverse Event	Exposure	Slope	P-value
Nausea any grade	AUC_{ss} of selumetinib (nM*h)	2.74E-04	0.0520
Nail disorders any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	3.78E-03	0.0615
Muscular toxicity any grade	AUC_{ss} of selumetinib (nM*h)	2.57E-04	0.0693
Constipation any grade	AUC_{ss} of selumetinib (nM*h)	2.82E-04	0.0785
Cardiac toxicity any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	3.18E-03	0.0787
Neutropenic events any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	5.77E-03	0.1269
Muscular toxicity any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	2.56E-03	0.1279
Lymphopenic events any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	5.65E-03	0.1342
Hepatotoxicity any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	2.75E-03	0.1616
Erythropenic events any grade	AUC_{ss} of selumetinib (nM*h)	2.53E-04	0.1726
Hepatotoxicity any grade	AUC_{ss} of selumetinib (nM*h)	1.92E-04	0.1742
Rash non-acneiform any grade	AUC_{ss} of selumetinib (nM*h)	1.72E-04	0.1824
Dermatitis and Eczema any grade	AUC_{ss} of selumetinib (nM*h)	4.33E-04	0.2011
Ocular toxicity any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	-4.72E-03	0.2348
Rash non-acneiform any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	1.93E-03	0.2357
Neutropenic events any grade	AUC_{ss} of selumetinib (nM*h)	2.94E-04	0.2581
Oral mucositis any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	1.98E-03	0.3067
Rash acneiform any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	-1.64E-03	0.3109
Nausea any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	-1.54E-03	0.4223
Vomiting any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	-1.44E-03	0.4333
Erythropenic events any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	2.10E-03	0.4462
Ocular toxicity any grade	AUC_{ss} of selumetinib (nM*h)	-2.11E-04	0.5082
Dermatitis and Eczema any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	3.47E-03	0.5143
Skin infection any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	-1.76E-03	0.5452
Oral mucositis any grade	AUC_{ss} of selumetinib (nM*h)	7.86E-05	0.5871
Cardiac toxicity any grade	AUC_{ss} of selumetinib (nM*h)	6.31E-05	0.6250
Vomiting any grade	AUC_{ss} of selumetinib (nM*h)	5.66E-05	0.6695
Diarrhea any grade	AUC_{ss} of selumetinib (nM*h)	4.61E-05	0.7059
Skin infection any grade	AUC_{ss} of selumetinib (nM*h)	7.20E-05	0.7133
Rash acneiform any grade	AUC_{ss} of selumetinib (nM*h)	4.31E-05	0.7290
Lymphopenic events any grade	AUC_{ss} of selumetinib (nM*h)	3.36E-05	0.9211
Diarrhea any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	7.14E-05	0.9639
Nail disorders any grade	AUC_{ss} of selumetinib (nM*h)	-5.60E-06	0.9700
Constipation any grade	AUC_{ss} of N-desmethyl selumetinib (nM*h)	8.84E-05	0.9705

AUC_{ss} = area under the curve under steady state conditions.

2.4.3. Discussion on clinical pharmacology

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 the KOMET study was already discussed and considered adequate during the original MAA procedure and subsequent applications.

No ISR were performed for the pivotal study. However, this issue will not be pursued as previous ISR analysis from the initial MAA or subsequent variations were shown to be satisfactory.

Based on NCA approach, following multiple doses of selumetinib, absorption was reasonably rapid with a median T_{max} achieved at 1.5 h. Geometric mean C_{max} and AUCtau were 789 ng/mL with a moderate variability (48.8%) and 2986 ng.h/mL (41.6%). These PK parameters were satisfactorily reported in the SmPC.

For comparison, in paediatric patients, T_{max} was achieved at 1-1.5 h, geometric mean C_{max} and AUC0-6h were 798 ng/mL and 1958 ng.h/mL (Initial CMA, Sum Clin Pharm Appendix B), respectively. In adults, geometric mean of AUC0-6h was 2224 ng.h/mL. A statement was added in section 5.2 of the SmPC indicating that the PK of selumetinib in paediatric patients aged 3 to < 18 years and adult patients with NF1-iPN are comparable, this is agreed. In adult patients (≥ 18 years old), at a dose level of 25 mg/m^2, selumetinib has an apparent oral clearance of 14.1 L/h, mean apparent volume of distribution at steady state of 126.1 L and mean elimination half-life of ~9.0 hours.

The mean apparent volume of distribution at steady state of selumetinib across 20 to 30 mg/m^2 ranged from 78 to 171 L in paediatric patients. Comparable values were observed in adult patients across 25 mg/m^2 and ranged from 40 to 3710 L. These values indicate moderate distribution into tissue.

The updated PPK model with PK data from adult subjects of the KOMET study is considered to be fit for purpose. The developed analysis has a low impact and was used in section 5.2 of the SmPC to inform on selumetinib T1/2 estimated at 9.0 h.

According to the KOMET study design, "rich PK sampling" has been performed at C1D8, therefore after reaching steady-state. In the KOMET study, at the recommended dosage of 25 mg/m2 twice daily in adult patients (≥ 18 years old), the geometric mean (geometric coefficient of variation [gCV%]) maximum plasma concentration (C_{max}) was 789 (47%) ng/mL and the area under the plasma drug concentration curve (AUC_{0-12}) was 2986 (43%) ng.h/mL at steady-state.

Across all ages, the minimal accumulation range was 1.2 to 1.5 following administration of selumetinib. Overall the PK of selumetinib in adult NF1-iPN patients can be considered comparable to children aged 3 to <18 years.

The developed PPK model can adequately describe the PK data from the KOMET study. Fixed and random effects were estimated with a good precision (RSE < 25%). RUV was moderately high 64%. Eta shrinkage was reasonable <25% on PK parameter of interest, therefore EBE (post-hoc) for ER can be considered reliable.

Predicted PK metrics by the PPK model were generally close to those estimated by NCA approach for C_{maxss} (745 vs 789 ng/mL) and AUC_{tau} (3380 vs 2980 ng.h/mL).

Instead of AUCss of selumetinib which have been shown to have a relationship with ORR in the initial MAA in the paediatric population, exploratory box-plots suggest unexpected trends with C_{maxss} of selumetinib, N-desmethyl selumetinib.

Upon request, additional analyses (logistic regression) investigating the relationship between C_{maxss} selumetinib, N-desmethyl selumetinib, total moiety and potency adjusted total moiety and efficacy (ORR, PAINS-pNF score, PlexiQoL score)/safety endpoints were performed by the applicant.

Although these post-hoc regression analyses were conducted without statistical power consideration or multiplicity adjustment (to the CHMP's knowledge these considerations were not taken into account at the time of the MAA to select the AUCss as the metric of interest on a dataset from an independent central review), a significant relationship was identified for C_{maxss} (selumetinib, N-desmethyl selumetinib) with ORR. For the time being, the fact that C_{maxss} seems to be associated with ORR have no clinical implication for adults.

Similarly, for safety endpoints C_{maxss} selumetinib and N-desmethyl selumetinib were identified to have a significant relationship with muscular toxicity of any grade and cardiac toxicity of any grade, respectively. However, for this last analysis both muscular and cardiac toxicities encompass several kinds of events from which no firm conclusions can be drawn.

2.5. Conclusion on clinical pharmacology

Overall the PK of selumetinib and N-desmethyl selumetinib can be considered comparable between adult and paediatric patients aged 3 to < 18 years following multiple dosing of 25 mg/m2 BID.

2.6. Clinical efficacy

2.6.1. Dose response study

The dose used in the pivotal study for this indication was 25 mg/m^2 and was the same than in Koselugo initial MAA. Description of the D1532C00057 SPRINT Phase I is included in section 2.51 of Koselugo initial European public assessment report. Exposure responses analyses of KOMET study are presented in section 2.3.4 of this report.

2.6.2. Main study

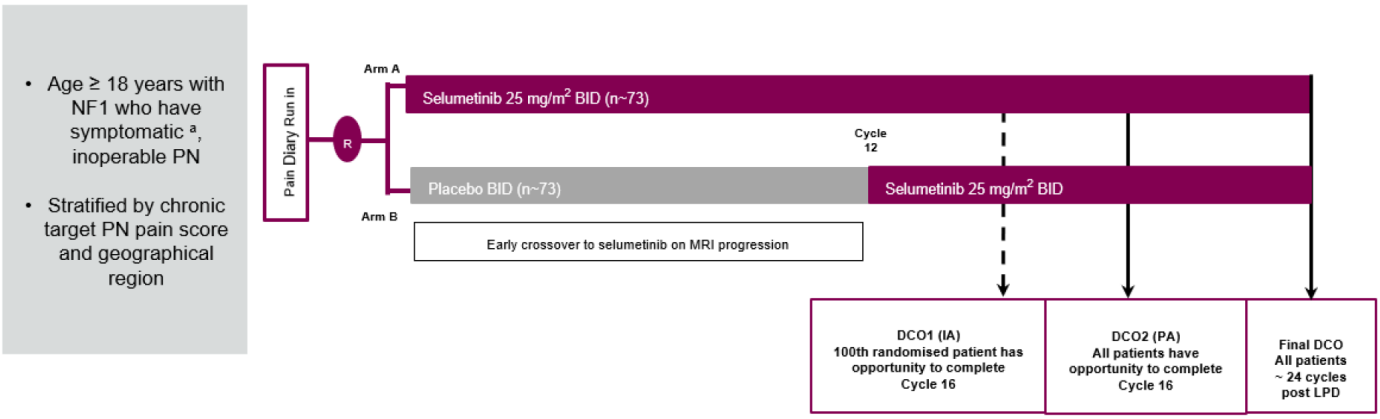
A Phase III, Multicentre, International Study with a Parallel, Randomized, Double-blind, Placebo-controlled, Two-arm Design to Assess the Efficacy and Safety of Selumetinib in Adult Participants with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET)

Methods

Design

The study consisted of a Screening Period (up to 28 days), a Randomized Period (up to twelve 28-day cycles of study intervention) followed by an Open-label Period (participants continue until disease progression occurs as judged by the investigator or until meeting any other discontinuation criteria) (Figure 14).

Figure 14: Schematic of Study Design



[a] Symptoms may include (but not limited to) pain, motor morbidity, disfigurement

Participants were randomized in a 1:1 ratio to one of the following treatment groups: selumetinib 25 mg/m² orally bid or placebo orally bid.

Randomization was stratified by average baseline PAINS-pNF chronic target PN pain score (< 3 and ≥ 3) and geographical region (Europe, China, Japan, and Rest of World). The number of participants randomized was planned to be capped at approximately 106 participants with an average baseline PAINS-pNF chronic target PN pain score ≥ 3 and approximately 40 participants with an average baseline PAINS-pNF chronic target PN pain score < 3.

Tumour response was evaluated at baseline and while on treatment after every 4 cycles for 2 years, and then every 6 cycles.

Three milestones were planned:

- DCO1: 100th randomized patients completed Cycle 16
- DCO2: all patients completed Cycle 16
- Final DCO all patients completed 24 cycles LPD.

Study participants

Main inclusion criteria

1- Participant ≥ 18 years at the time of screening.

2- All participants must have a diagnosis of NF1 with symptomatic, inoperable PN where

(a) Participants must have PN and at least one other diagnostic criterion for NF1 (Legius et al 2021):

(i) Six or more café-au-lait spots (> 5 mm in greatest diameter in pre-pubertal participants or > 15 mm in greatest diameter in post-pubertal participants)

(ii) Freckling in the axillary or inguinal region - At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral

(iii) Two or more iris Lisch nodules identified by slit lamp examination or 2 or more choroidal abnormalities—defined as bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging

(iv) Optic pathway glioma

(v) A distinctive osseous lesion such as: sphenoid dysplasia, anterolateral bowing of the tibia, or pseudoarthrosis of a long bone- Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital PN.

(vi) A NF1 heterozygous pathogenic variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

(vii)A parent with NF1 by the above criteria

(b) A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves 2 or more levels with connection between the levels or extending laterally along the nerve. A histologic confirmation of the PN is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant transformation of a PN is clinically suspected.

(c) Inoperable is defined as a PN that cannot be completely surgically removed without a risk of substantial morbidity (including significant bleeding or damage to nerves and/or surrounding vital structures) due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN; or unacceptable risk from the general anaesthetic as assessed by the investigator.

(d) Symptomatic is defined as clinically significant symptoms caused by the PN, as judged by the investigator; symptoms may include, but are not limited to, pain, motor dysfunction, and disfigurement.

3- Eastern Cooperative Oncology Group performance status of 0 or 1

4- Participants must have completed a pain diary (PAINS-pNF) with a documented chronic target PN pain score for at least 4 days out of 7 days for at least 2 weeks during the screening period. Participants must have stable chronic PN pain medication use at baseline, defined as no clinically significant changes to prescribed chronic PN pain medication within 28 days prior to study enrolment or planned at the time of study enrolment

5- Participants must have at least one measurable PN, defined as a PN of at least 3 cm measured in one dimension.

Main exclusion criteria

1- As judged by the investigator, any evidence of, or history of allogenic organ transplant, which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.

2- Refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of selumetinib.

3- Participants with confirmed or suspected malignant glioma or MPNST. Participants with low grade glioma (including optic glioma) not requiring systemic therapy or radiation therapy are permitted.

4- Prior exposure to MEK inhibitors.

5- Receipt of the last dose of systemic PN target treatment (including chemotherapy, immunotherapy, targeted therapy, biologic therapy, or monoclonal antibodies) within 4 weeks prior to the first dose of study intervention or 5 half-lives of the respective systemic PN target treatment, whichever is longer.

6- Has received radiotherapy in the 6 weeks prior to the start of study intervention or any prior radiotherapy directed at the target or non-target PN.

7- Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

Treatments

During the **randomized Period** participants received study intervention (selumetinib or placebo) for up to twelve 28-day cycles. Treatment after completion of 12 cycles of study intervention was **open-label**: participants randomized to the selumetinib group continued to receive selumetinib and participants randomized to the placebo group (referred to as the placebo/selumetinib group) were crossed over to selumetinib treatment. All participants were permitted to continue treatment in the Open-label Period until disease progression or discontinuation criteria are met (patient was no longer deriving clinical benefit, experienced unacceptable toxicity, patient decision, PN progression, or at the discretion of the investigator).

Participants received selumetinib orally bid approximately 12 hours apart but no less than 6 hours apart, on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing). After implementation of CSP amendment version 4, participants were no longer required to observe the fasting restriction described above after completion of Cycle 24 (i.e., Cycle 25 Day 1 and beyond).

Table 11: Body Surface Area Dosing Guidelines

Body Surface Area (m^2)	Selumetinib Starting Dose (mg) [a]	
	AM	PM
1.1 to 1.29	30	30
1.3 to 1.49	35	35
1.5 to 1.69	40	40
1.7 to 1.89	45	45
≥ 1.90	50	50

[a] Actual dose in milligram (capsule sizes 10 and 25 mg) administered every 12 hours to achieve a dosage of 25 mg/m^2 bid.

Objectives and outcomes/endpoints

Objectives	Estimands Descriptions/Endpoints
Primary	
To compare the effect of selumetinib relative to placebo by assessment of confirmed partial and complete response rate (ORR) by end of Cycle 16 using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN	ORR was defined as the proportion of participants who have a confirmed CR (defined as disappearance of the target PN, confirmed by a consecutive scan within 3 to 6 months after the first response) or confirmed PR (defined as a target PN volume decrease ≥ 20%, compared to baseline, confirmed by a consecutive scan within 3 to 6 months after the first response) by end of Cycle 16 as determined by ICR per REiNS criteria. Data obtained while on-treatment from first dose up until progression (if progression occurs prior to end of Cycle 16), or the last evaluable assessment up to and including end of Cycle 16 in the absence of progression, was included in the assessment of ORR. The measure of interest was the difference in ORR.
Key Secondary	
To compare the effect of selumetinib relative to placebo by assessment of change in chronic target PN pain intensity from baseline in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline	Difference of the means in the change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib and placebo amongst participants with a PAINS-pNF chronic target PN pain intensity score ≥ 3 at baseline, and at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score, regardless of changes to the participants' chronic PN pain medication (treatment policy strategy).
To compare the effect of selumetinib relative to placebo by assessment of change in HRQoL from baseline in participants with NF1 who have symptomatic, inoperable PN	Difference in change from baseline in PlexiQoL total score between selumetinib and placebo at Cycle 12 amongst participants with a PlexiQoL total score at baseline and at least one post-baseline total score
Secondary	

To demonstrate the effectiveness of selumetinib by assessment of confirmed partial and complete response rate (ORR) using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN	This ORR analysis included all participants randomized to selumetinib who received at least one dose of selumetinib, i.e., single-arm assessment of ORR. Data obtained while on treatment from first selumetinib dose up until progression, or the last evaluable assessment in the absence of progression, was included in the assessment of ORR.
To demonstrate the effectiveness of selumetinib by assessment of DoR in participants with NF1 who have symptomatic, inoperable PN	DoR was defined as the time from the date of first documented response (which was subsequently confirmed) until date of documented progression by ICR per REiNS criteria or death due to any cause. The analysis included all participants randomized to selumetinib who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to study intervention discontinuation. DoR was derived using while on-treatment MRI volumetric assessments.
To demonstrate the effectiveness of selumetinib by assessment of TTR in participants with NF1 who have symptomatic, inoperable PN	TTR was defined as the time from date of first selumetinib dose until the date of first documented objective response (which was subsequently confirmed), by ICR per REiNS criteria. The analysis included all participants randomized to selumetinib who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to selumetinib discontinuation. Data obtained from first dose up until progression, or the last evaluable assessment in the absence of progression, was included in the assessment of TTR. TTR was derived using while on-treatment MRI volumetric assessments.
To demonstrate the effect of selumetinib relative to placebo by assessment of percentage change from baseline in target PN volume in participants with NF1 who have symptomatic, inoperable PN	Difference in best percentage change from baseline in target PN volume by ICR per REiNS criteria between selumetinib and placebo during the Randomized Period. The analysis included all participants randomized to study intervention. The best percentage change from baseline in target PN volume was derived using while on-treatment MRI volumetric assessments during the Randomized Period.
To compare the effect of selumetinib relative to placebo by assessment of chronic target PN pain palliation and time to chronic target PN pain palliation in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline	Chronic target PN pain palliation was defined as improvement of ≥ 2 in average cycle PAINS-pNF chronic target PN pain intensity score and no increase in chronic PN pain medication compared to baseline for that cycle. Pain palliation was assessed in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline. • Difference in proportion of participants with chronic target PN pain palliation between selumetinib and placebo at post-baseline cycles and overall, over the Randomized Period. • Time to chronic target PN pain palliation was defined as the time from the first dose of study intervention until the cycle of chronic target PN pain palliation.
To compare the effect of selumetinib relative to placebo by assessment of pain medication compared with baseline	Difference in change from baseline in pain medication use (as reported using the eDiary and as assessed by the investigator) between

	selumetinib and placebo at post-baseline cycles and overall, over the Randomized Period.
To compare the effect of selumetinib relative to placebo by assessment of pain interference compared with baseline	Difference in change from baseline in PII-pNF pain interference total score between selumetinib and placebo at post-baseline cycles and overall over the Randomized Period.
To compare the effect of selumetinib relative to placebo by assessment of physical functioning compared with baseline	Difference in change from baseline in PROMIS Physical Function scores between selumetinib and placebo at postbaseline cycles and overall over the Randomized Period.
To compare the effect of selumetinib relative to placebo by further assessment of HRQoL compared with baseline	Difference in change from baseline in the Skin Sensations domain from the PedsQL (NF1 module acute Version 3.0 – adult report) between selumetinib and placebo at post-baseline cycles and overall over the Randomized Period
To compare the effect of selumetinib relative to placebo by assessment of health status compared with baseline	Difference in change from baseline in EQ-5D-5L (standardised measure of health status) between selumetinib and placebo at post-baseline cycles and overall over the Randomized Period. Five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).
	Difference in change from baseline in EQ-VAS between selumetinib and placebo at post-baseline cycles and overall over the Randomized Period.
To evaluate the effect of selumetinib by assessment of physical functioning compared with baseline	Change from baseline in PlexiQoL
	Change from baseline in the Skin Sensations domain from the PedsQL (NF1 module acute Version 3.0 – adult report)
Pharmacokinetic	
To assess the PK of selumetinib	• Plasma concentrations and PK parameters of selumetinib including, but not limited to: – C_{max}, AUC(0-6), AUC(0-8), AUClast, CL/F, Vss/F, t_{max}, t_{last} derived after multiple dose administration Plasma concentrations and PK parameters of N-desmethyl selumetinib including, but not limited to: – C_{max}, AUC(0-6), AUC(0-8), AUClast, t_{max}, tlast derived after multiple dose administration – MPAUC and MPC_{max} after multiple dose administration • Population PK-pharmacodynamic analyses were completed to investigate the selumetinib exposure-response relationship for safety and efficacy

Sample size

Approximately 212 participants were planned to be enrolled to achieve approximately 146 participants randomly assigned 1:1 to study intervention (selumetinib or placebo). With a sample size of 73 participants per group, a Fisher's exact test with a 2-sided alpha of 5% would have > 99% power to

detect the difference between the selumetinib ORR of 20% and the placebo ORR of 0%. The ORR of 20% in the selumetinib group by end of Cycle 16 was assumed from ad hoc modelling performed using the SPRINT NCI and ICR data and the Adult NF1 NCI study response rates.

Forty-two participants per group were required for the study to have 90% power to detect a treatment difference of ≥ -2 in the first key secondary endpoint change from baseline of PAINS-pNF chronic target PN pain score (assuming an SD of 2.8) in favour of selumetinib compared with placebo at a 2-sided alpha level of 5%. To allow for approximately 20% drop out (i.e., participants without at least one postbaseline average cycle PAINS-pNF chronic target PN pain score), 106 participants with a baseline PAINS-pNF chronic target PN pain score of ≥ 3 will be randomized in a 1:1 selumetinib: placebo allocation.

By assuming a 20% drop out (i.e., participants without at least one post baseline PlexiQoL total score), 58 participants per group would provide at least 80% power to detect a treatment difference at Cycle 12 in the second key secondary endpoint change from baseline of PlexiQoL total score (assuming an SD of 2.3) of at least -1.2 in favour of selumetinib compared with placebo at a 2-sided alpha level of 5%.

Randomisation

Eligible participants randomized in a 1:1 ratio to one of the following treatment groups: selumetinib 25 mg/m2 orally bid or placebo orally bid. Randomization was stratified by average baseline PAINS-pNF chronic target PN pain score (< 3 and ≥ 3) and geographical region (Europe, China, Japan, and Rest of World).

Blinding (masking)

The actual treatment given to participants was determined by the randomisation scheme in the Interactive Response Technology (IRT). The randomisation scheme will be produced by a computer software programme that incorporates a standard procedure for generating randomisation numbers. One randomisation list is produced for each of the randomisation strata. A blocked randomisation was generated, and randomisation balanced within the IRT at the central level.

Randomisation codes were assigned strictly sequentially, within each stratum, as participants become eligible for randomisation. The IRT provided the kit identification number to be allocated to the participant at the randomisation visit and subsequent treatment visits. For participants assigned to placebo at randomisation, the cross-over to selumetinib occurred after the end of Cycle 12.

Statistical methods

The analysis populations are defined below:

Table 12: Populations for Analysis

Analysis Set	Description
Enrolled	All participants who signed the ICF.
FAS	All participants who were randomized to study intervention in the study.
Pain FAS	All participants with a baseline PAINS-pNF chronic target PN pain intensity score ≥ 3.
Selumetinib FAS	All participants who were randomized to selumetinib.

Extended Selumetinib FAS	All participants who were randomized to study intervention who received at least one dose of selumetinib, i.e., including participants randomized to placebo who crossover to selumetinib treatment.
SAF	All enrolled participants who received any amount of study intervention (selumetinib or placebo).
Randomized Period SAF	All enrolled participants who received any amount of study intervention (selumetinib or placebo) during the Randomized Period.
On-selumetinib SAF	All enrolled participants who received any amount of selumetinib during the On-selumetinib Period.
PK analysis set	All randomized participants who took at least one dose of study intervention for whom any post-dose reportable PK concentration was available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses.
Fed FAS	All participants who were randomized to study intervention in the study, who have received at least one dose of selumetinib in fed state, and who had at least one evaluable scan per ICR assessment in fed state at end of Cycle 30 or later.

KOMET Study Statistical Methods

The primary analysis of efficacy was based on data from all randomized participants (Full Analysis Set - FAS). A significance level of 0.05 (2-sided) was initially assigned to test the primary endpoint. A split-alpha strategy was used, with 0.003 (2-sided) allocated to the interim analysis (DCO1) and the remaining 0.047 (2-sided) allocated to the primary analysis (DCO2). Statistical significance was not reached at DCO1, so the remaining alpha was used for the primary analysis of ORR by the end of Cycle 16 at DCO2. Once statistical significance for the primary endpoint was reached, the remaining alpha was allocated to the first key secondary endpoint. The p-value for the second key secondary endpoint could only be interpreted nominally.

All tests were 2-sided, and no adjustments for multiplicity were made for other efficacy endpoints, making p-values nominal. Similarly, p-values for sensitivity and supportive analyses were also nominal.

Primary Endpoint: ORR by the End of Cycle 16

The primary endpoint, ORR by the end of Cycle 16, was defined as the proportion of participants with a confirmed complete response (CR) or partial response (PR) based on blinded ICR REiNS assessment using volumetric MRI analysis. CR was defined as the disappearance of the target PN, confirmed by a consecutive scan within 3 to 6 months after the first response, and PR was defined as a target PN volume decrease of ≥ 20%, compared to baseline, confirmed by a consecutive scan within 3 to 6 months after the first response.

The ORR by the end of Cycle 16 was calculated using participant responses derived from both scheduled and unscheduled MRI scans taken while on treatment. Data were included until progression occurred, or until the last evaluable assessment up to and including Cycle 16 Day 28 if progression did not occur.

The primary analysis was performed using a Fisher's exact test with a significance level of alpha of 0.047 (2-sided). Additionally, the ORR for each treatment group was presented with the corresponding 2-sided 95% confidence interval (CI) based on the Clopper-Pearson method, and the risk difference was presented with its 95% CI using the Miettinen-Nurminen (score) method. Sensitivity analyses were performed, including scans during long-term interruptions and supplementary analyses based on non-scaled volumes after DCO1.

First Key Secondary Endpoint: Change from Baseline in PAINS-pNF Chronic Target PN Pain Intensity Score at Cycle 12

The first key secondary endpoint was the mean change from baseline in PAINS-pNF chronic target PN pain intensity at Cycle 12. PAINS-pNF pain intensity scores for each cycle were derived as the average of the available daily pain scores, provided at least 4 daily scores were non-missing in at least 3 non-overlapping 7-day periods. The baseline score was derived similarly from the Screening Period.

The primary analysis was performed using a Mixed Model for Repeated Measures (MMRM), adjusting for treatment group, cycle, geographic region, and baseline PAINS-pNF chronic target PN pain intensity score. Sensitivity analyses were conducted to evaluate the robustness of the estimates, using multiple imputation techniques for missing data.

Second Key Secondary Endpoint: Change from Baseline in PlexiQoL Total Score at Cycle 12

The second key secondary endpoint was the mean change from baseline in the PlexiQoL total score at Cycle 12. The primary analysis included all data obtained during the Randomized Period.

The mean change from baseline was estimated using MMRM, adjusting for treatment group, cycle, and stratification factors, with baseline PlexiQoL total score as a covariate. A supplementary analysis was performed for the Pain FAS population with at least one evaluable post-baseline assessment. Sensitivity analyses were conducted using similar approaches as for the first key secondary endpoint.

Other Efficacy Endpoints

Secondary efficacy endpoints included single-arm ORR, Duration of Response (DoR), Time to Progression (TTP), Time to Response (TTR), and Progression-Free Survival (PFS), all analysed in the Selumetinib FAS. Best percentage change from baseline in target PN volume and PFS were analysed using ANCOVA with baseline target PN volume as a covariate and treatment as a fixed factor.

Chronic target PN pain palliation and chronic pain medication decrease were analysed with a generalized linear mixed model adjusted by treatment group, cycle, baseline chronic PN pain analgesic WHO ladder score, and geographical region.

Time to chronic target PN pain palliation was analysed using Kaplan-Meier and log-rank methods, stratified by geographical region, with Cox regression models used for additional analysis.

Subgroup Analysis

Subgroup analyses were performed to assess the homogeneity of the treatment effect. Subgroups were defined based on demographic factors (age, sex, race, ethnicity) and baseline characteristics (target PN volume and location). The primary analysis of ORR and the key secondary endpoints (PAINS-pNF and PlexiQoL) was repeated for each subgroup. For subgroups with fewer than 14 participants, only descriptive statistics were provided.

Subgroup analyses were exploratory, and no multiplicity adjustment was made. P-values were nominal, with statistical significance interpreted descriptively.

Post Hoc Analyses

Additional analyses not specified in the SAP were performed to facilitate data interpretation. These included:

- A line plot showing the raw mean changes from baseline for PAINS-pNF chronic target PN pain intensity scores over the entire study period by treatment group, including the means observed after the placebo participants crossed over to selumetinib.

- Shift tables of chronic and spike PN pain medication strongest analgesic ladder classes from baseline to Cycle 12 by treatment group.
- MMRM analyses of change from baseline in PII-pNF pain interference score repeated in the FAS by the individual items.
- Bar charts showing the observed percentage of FAS participants with pain medication decrease as reported in the e-diary, by treatment group over the randomized period and over the entire study period for the selumetinib arm.

Results

Participant flow

Table 13: Participant Disposition (All Enrolled Participants)

	Selumetinib	Placebo/ Selumetinib	Total
	n (%)	n (%)	n (%)
Participants enrolled [a]	NA	NA	184
Participants randomized	71 (100)	74 (100)	145 (100)
Participants who were not randomized	NA	NA	39
Screen failure	NA	NA	28
Pains-PNF score < 3 strata closed	NA	NA	10
Withdrawal by participant	NA	NA	1
Participants who received study intervention	71 (100)	74 (100)	145 (100)
Participants who crossed over to selumetinib	NA	66 (89.2)	66 (45.5)
Started selumetinib treatment prior to end of Cycle 12 visit	NA	3 (4.1)	3 (2.1) [b]
Started selumetinib treatment after end of Cycle 12 visit	NA	63 (85.1)	63 (43.4)
Participants ongoing study intervention at DCO date	53 (74.6)	59 (79.7)	112 (77.2)
Participants who discontinued study intervention	18 (25.4)	15 (20.3)	33 (22.8)
AE	10 (14.1)	6 (8.1)	16 (11)
Participant decision	5 (7.0)	9 (12.2)	14 (9.7)
Subjective disease progression	2 (2.8)	0	2 (1.4)
Participant lost to follow-up	1 (1.4)	0	1 (0.7)
Participants who discontinued study intervention prior to end of Cycle 12 visit	13 (18.3)	9 (12.2)	22 (15.2)
AE	7 (9.9)	5 (6.8) [c]	12 (8.3)
Participant decision	4 (5.6)	4 (5.4)	8 (5.5)
Subjective disease progression	1 (1.4)	0	1 (0.7)
Participant lost to follow-up	1 (1.4)	0	1 (0.7)
Participants ongoing study at data cut-off date	54 (76.1)	60 (81.1)	114 (78.6) [d]
Participants who terminated study	17 (23.9)	14 (18.9)	31 (21.4) [d]
AE	10 (14.1)	6 (8.1)	16 (11.0)
Withdrawal by participant	3 (4.2)	6 (8.1)	9 (6.2)
Lost to follow-up	1 (1.4)	1 (1.4)	2 (1.4)
Other	1 (1.4)	1 (1.4)	2 (1.4)
Progressive disease	2 (2.8)	0	2 (1.4)

a Informed consent received.

b Two participants due to PD as determined by ICR and 1 participant crossed over after Cycle 8 due to an administrative error.

c One participant in the placebo group crossed over to receive selumetinib treatment after Cycle 8 in the Randomized Period due to PD and then subsequently discontinued selumetinib treatment due to an AE during the Open-label Period prior to completing 12 cycles in the study.
d At the time of the DCO date, 2 participants had discontinued study intervention and were ongoing in the study in the Safety Follow-up Period.
Based on DCO date 05 August 2024

Among the three participants who crossed over prior to the end of Cycle 12 visit; 2 due to PD as assessed by ICR per REiNS criteria and 1 crossed over after Cycle 8 due to an administrative error.

Recruitment

Results for the planned DCO2 Primary Analysis are presented and includes the study period from 19 November 2021 (first participant signed informed consent) through the DCO date of 05 August 2024 (after the last treated participant had the opportunity to complete the end of Cycle 16 assessment).

Participants were enrolled in 33 sites in 13 countries (Australia, Brazil, Canada, China, France, Germany, Italy, Japan, Poland, Russia, Spain, United Kingdom, and US).

Conduct of the study

Protocol amendments

Since the original CSP (dated 01 April 2021), three global CSP amendments were made for this study.

Amendment 3 (Version 4.0) Global 03Nov2023

The main purpose of this amendment was to remove the fasting restriction after end of Cycle 24; revise the first key secondary endpoint estimand; and include an additional key secondary endpoint.

Amendment 2 (Version 3.0) Global 07Nov2022

The main purpose of this amendment was the addition of an exploratory biomarker analysis.

Amendment 1 (Version 2.0) Global 25Jan2022

The main purpose of the amendment was to revise the primary objective to be comparative relative to placebo.

Protocol deviations

Important deviations were defined as any non-compliance that might significantly impact the reliability of the study data or that may significantly affect a participant's rights, safety, or well-being.

Table 14: Summary of Important protocol deviations

Deviation type	Selumetinib arm	Control arm
Exclusion criteria	2	3
Inclusion criteria	1	0
Prohibited medication received during the Randomized Period	5	4
Incorrect dose of study intervention received during the Randomized Period	8	3
Incorrect dose of study intervention received during the Open-label Period	5	NA
Deviation from protocol on dose reduction instruction Randomized Period	1	0

Deviation type	Selumetinib arm	Control arm
Deviation from protocol on dose reduction instruction Open-label Period	3	NA
Deviation from protocol on dose interruption		2
ICF	1	2
Delayed reporting of SAE	3	0
Deviation from schedule of assessment		
Missed creatinine kinase testing during the Randomized Period	1	2
Cycle 16 Day 28 Visit performed out of window	8	8
ECHO not performed at the Safety Follow-up Visit	0	1

Five participants had an IPD related to exclusion criteria

- 2 participants in the placebo group had uncontrolled hypertension; 1 participant had high BP at Screening which was attributed to anxiety by the investigator, but did not have a history of cardiovascular disease and 1 participant had normal BP at the Screening visit but had a history of hypertension (Exclusion Criterion 10h).
- 2 participants in the selumetinib group took herbal supplements or medications at doses known to be strong or moderate inhibitors of CYP2C19 within 14 days of first dose of study intervention (Exclusion Criterion 18).
- 1 participant in the placebo group had mean resting QTcF interval > 470 ms obtained from triplicate ECGs performed at rescreening (Exclusion Criterion 8). Overall, the investigator assessed the ECG as normal and not deemed as clinically significant.

All 9 participants (selumetinib: 5; placebo: 4) who had an IPD related to prohibited medication during the Randomized Period received strong or moderate inhibitors of CYP3A4 or CYP2C19 and did not reduce the dose of study intervention according to the protocol.

Baseline data

Demographics

Table 15: Demographic Characteristics (FAS)

		Selumetinib (N = 71)	Placebo (N = 74)	Total (N = 145)
Age (years) [a]	Mean	32.6	29.8	31.2
	SD	11.42	8.72	10.19
	Min	18	18	18
	Median	31	28	29
	Max	60	53	60
Sex, n (%)	Male	33 (46.5)	42 (56.8)	75 (51.7)
	Female	38 (53.5)	32 (43.2)	70 (48.3)
Race, n (%)	Asian	22 (31)	23 (31.1)	45 (31.0)
	Black or African American	6 (8.5)	3 (4.1)	9 (6.2)
	White	38 (53.5)	43 (58.1)	81 (55.9)
	Other	2 (2.8)	3 (4.1)	5 (3.4)

	Not reported	3 (4.2)	2 (2.7)	5 (3.4)
Ethnicity, n (%)	Hispanic or Latino	5 (7.0)	9 (12.2)	14 (9.7)
	Not Hispanic or Latino	63 (88.7)	63 (85.1)	126 (86.9)
	Missing	3 (4.2)	2 (2.7)	5 (3.4)
Geographical region, n (%) [b]	China	11 (15.5)	13 (17.6)	24 (16.6)
	Japan	7 (9.9)	8 (10.8)	15 (10.3)
	Europe [c]	31 (43.7)	30 (40.5)	61 (42.1)
	Rest of world [c]	22 (31)	23 (31.1)	45 (3.11)

a Age at screening

b Stratification factor
c Europe included France, Germany, Italy, Poland, Russia, Spain, and United Kingdom. Rest of world includes Australia, Brazil, Canada, and United States.
Based on DCO date 05 August 2024

Disease Characteristics

Table 16: Baseline Disease Characteristics – NF1 Diagnosis and Target PN (FAS)

	Selumetinib (N = 71)	**Placebo (N = 74)**	**Total (N = 145)**
	n (%)	**n (%)**	**n (%)**
Time from diagnosis of NF1 to start of study intervention (years)			
n	70 [a]	74	144
Mean (SD)	23.140	18.572	20.793
SD	13.4556	12.6994	13.2265
Median	23.014	18.739	20.957
Min, max	0.06, 60.87 [a]	0.04, 47.00	0.04, 60.87
Time from diagnosis of inoperable PN to start of study intervention (years)			
n	70 [b]	74	144
Mean	8.688	8.101	8.387
SD	11.4275	11.2717	11.3118
Median	2.509	2.278	2.327
Min, max	0.04, 45.89	0.03, 38.92	0.03, 45.89
Reasons PN inoperable, n (%)			
PN encasement of vital structures	19 (26.8)	25 (33.8)	44 (30.3)
PN close proximity to vital structures	36 (50.7)	40 (54.1)	76 (52.4)
PN invasiveness	32 (45.1)	34 (45.9)	66 (45.5)
High vascularity of the PN	19 (26.8)	25 (33.8)	44 (30.3)
Unacceptable risk from the general anaesthetic	1 (1.4)	0	1 (0.7)
Other	13 (18.3)	17 (23.0)	30 (20.7)
Missing	1 (1.4)	0	1 (0.7)
NF1 diagnostic criteria [b], n (%)			

	Selumetinib (N = 71)	Placebo (N = 74)	Total (N = 145)
	n (%)	n (%)	n (%)
Any cafe-au-lait macules [c]	56 (78.9)	54 (73.0)	110 (75.9)
Bilateral cafe-au-lait spots [c]	42 (59.2)	46 (62.2)	88 (60.7)
Freckling in axillary or inguinal region	49 (69)	49 (66.2)	98 (67.6)
Bilateral freckles in axilla or groin	45 (63.4)	43 (58.1)	88 (60.7)
Optic pathway glioma	7 (9.9)	7 (9.5)	14 (9.7)
≥ 2 iris Lisch nodules or ≥ 2 choroidal abnormalities	30 (42.3)	33 (44.6)	63 (43.4)
A distinctive osseous lesion	11 (15.5)	15 (20.3)	26 (17.9)
A NF1 heterozygous pathogenic variant	29 (40.8)	21 (28.4)	50 (34.5)
A parent with NF1 by the above criteria	16 (22.5)	23 (31.1)	39 (26.9)
Missing	1 (1.4)	1 (1.4)	2 (1.4)
Target PN volume, mL			
Mean (SD)	836.27 (2369.340)	539.53 (927.236)	Not calculated
Median	110.18	221.85	Not calculated
Min, max	3.3, 13574.9	9.1, 5621.9	Not calculated
Target PN overall location, n (%)			
Neck/trunk	8 (11.3)	11 (14.9)	19 (13.1)
Trunk/extremity	16 (22.5)	11 (14.9)	27 (18.6)
Head and neck	7 (9.9)	5 (6.8)	12 (8.3)
Head	5 (7)	7 (9.5)	12 (8.3)
Extremity	13 (18.3)	18 (24.3)	31 (21.4)
Body	1 (1.4)	2 (2.7)	3 (2.1)
Trunk	21 (29.6)	19 (25.7)	40 (27.6)
Other	0	1 (1.4)	1 (0.7)
Target PN symptoms [e], n (%)			
Any symptoms	71 (100)	74 (100)	145 (100)
Vision loss	2 (2.8)	3 (4.1)	5 (3.4)
Facial motor dysfunction	7 (9.9)	3 (4.1)	10 (6.9)
Auditory loss	2 (2.8)	0	2 (1.4)
Difficulty swallowing	2 (2.8)	2 (2.7)	4 (2.8)
Abnormal speech	0	1 (1.4)	1 (0.7)
Airway obstruction	2 (2.8)	3 (4.1)	5 (3.4)
Respiratory compromise	1 (1.4)	1 (1.4)	2 (1.4)
Bladder dysfunction	1 (1.4)	2 (2.7)	3 (2.1)
Bowel dysfunction	2 (2.8)	2 (2.7)	4 (2.8)

	Selumetinib (N = 71)	Placebo (N = 74)	Total (N = 145)
	n (%)	n (%)	n (%)
Motor weakness	14 (19.7)	19 (25.7)	33 (22.8)
Decreased range of motion	19 (26.8)	19 (25.7)	38 (26.2)
Sensory deficit	8 (11.3)	13 (17.6)	21 (14.5)
PN-related disfigurement	23 (32.4)	17 (23.0)	40 (27.6)
Pain	62 (87.3)	61 (82.4)	123 (84.8)
Other symptom	12 (16.9)	19 (25.7)	31 (21.4)
Overall target PN morbidity type [e]			
Airway	3 (4.2)	3 (4.1)	6 (4.1)
Bowel/bladder	2 (2.8)	2 (2.7)	4 (2.8)
Disfigurement	23 (32.4)	17 (23.0)	40 (27.6)
Motor	30 (42.3)	27 (36.5)	57 (39.3)
Pain	62 (87.3)	61 (82.4)	123 (84.8)
Vision	3 (4.2)	3 (4.1)	6 (4.1)
Other	11 (15.5)	20 (27.0)	31 (21.4)
Number of target PN morbidities			
Mean (SD)	1.9 (1.03)	1.8 (0.91)	1.8 (0.96)
Median (min, max)	2 (1, 5)	2 (1, 5)	2 (1, 5)
Baseline PAINS-pNF chronic target PN pain intensity score [f]			
< 3	21 (29.6)	21 (28.4)	42 (29.0)
≥ 3	50 (70.4)	53 (71.6)	103 1.0)
Any non-target PN, n (%)			
No	53 (74.6)	44 (59.5)	97 (66.9)
Yes	18 (25.4)	30 (40.5)	48 (33.1)

a Time from diagnosis of NF1 to start of study intervention was > 60 years since it was calculated based on date of birth and age at screening was recorded on eCRF and not calculated.
b Participants could have had more than one NF1 diagnostic criteria.
c Only includes participants with ≥ 6 macules.
d Two participants in the selumetinib group had a value of zero in the table output due to formatting so the actual tumour volume values were truncated to zero.
e A participant could have had multiple symptoms and overall morbidity types.
f Stratification factor
Based on DCO date 05 August 2024

Numbers analysed

The analysis populations are defined in the Statistical methods

A total 145 randomized participants were included in the FAS and the Safety Set; 103 participants were in the Pain FAS and all 71 participants randomized to the selumetinib group were included in the Selumetinib FAS.

Table 17: Analysis Sets (All Enrolled)

	Selumetinib (N = 71)	Placebo / selumetinib (N = 74)	Total (N = 145)
Participants randomized	71	74	145
Participants included in FAS	71	74	145
Participants included in Pain FAS	50	53	103
Participants excluded from Pain FAS [a]	21	21	42
Participants included in Selumetinib FAS	71	NA	71
Participants included in Extended Selumetinib FAS	71	66	137
Participants excluded from Extended Selumetinib FAS [b]	0	8	8
Participants included in SAF	71	74	145
Participants included in Randomized Period SAF	71	74	145
Participants included in On-selumetinib SAF	71	66	137
Participants excluded from On-selumetinib SAF [b]	0	8	8
Participants included in PK analysis set	64	0	64
Participants excluded from PK analysis set [c]	7	74	81
Participants included in Fed FAS	4	5	9
Participants excluded from Fed FAS	67	69	136

[a] Pain threshold not reached.

[b] Participants did not cross over to Open-label Period.

[c] 5 participants due to no PK sample and 2 participants due to deviations that would significantly affect the PK analyses.

Based on DCO date 05 August 2024

Outcomes and estimation

Results in this section are presented as of 05 August 2024 DCO, unless otherwise specified.

Primary Endpoint – Objective Response Rate by End of Cycle 16

Table 18: Confirmed Objective Response Rate by End of Cycle 16, On-treatment MRI Volumetric Assessments Period (FAS)

Treatment Group	N	Number of Participants with Response [a]	Response Rate (%)	95% CI [b]	p-value [c]
Selumetinib	71	14	19.7	(11.2, 30.9)	
Placebo	74	4	5.4	(1.5, 13.3)	
Difference in response rate (%) [d]			14.3	(3.8, 25.8) [e]	0.0112

a Includes participants with a confirmed CR or confirmed PR as determined by ICR as per the REiNS criteria.
b 2-sided exact 95% CI calculated using the Clopper Pearson method.
c 2-sided p-value calculated using Fisher's exact method (alpha of 0.047) to test the hypotheses H0: ORR selumetinib = ORR placebo vs H1: ORR selumetinib ≠ ORR placebo.
d 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method.

e 2-sided 95% CI calculated using the Miettinen-Nurminen (score) method with adjustment for the stratification factors (geographical region: China/Europe/Japan/Rest of the world; baseline PAINS-pNF chronic target PN pain intensity score group: < 3/≥ 3) at randomization.
f 2-sided p-value calculated using Cochran-Mantel-Haenszel test with adjustment for the stratification factors (geographical region: China/Europe/Japan/Rest of the world; baseline PAINS-pNF chronic target PN pain intensity score group: < 3/≥ 3) at randomization.

Note: A positive difference in response rates favours selumetinib.
Based on DCO date 05 August 2024

Two of the 4 responders in the placebo group had onset of response at Cycle 12 Day 28, with the second scan at Cycle 16 Day 28 demonstrating confirmation, 4 cycles after the participants started selumetinib treatment (at the end of Cycle 12).

Sensitivity analysis

The analysis of ORR was repeated based on all on-treatment MRI volumetric assessments including scans during prolonged treatment interruption (> 28 continuous days of no study intervention); the results were the same as the primary analysis of ORR.

First key Secondary Endpoint : PAINS-pNF Chronic Target PN Pain Intensity Score
Randomized period

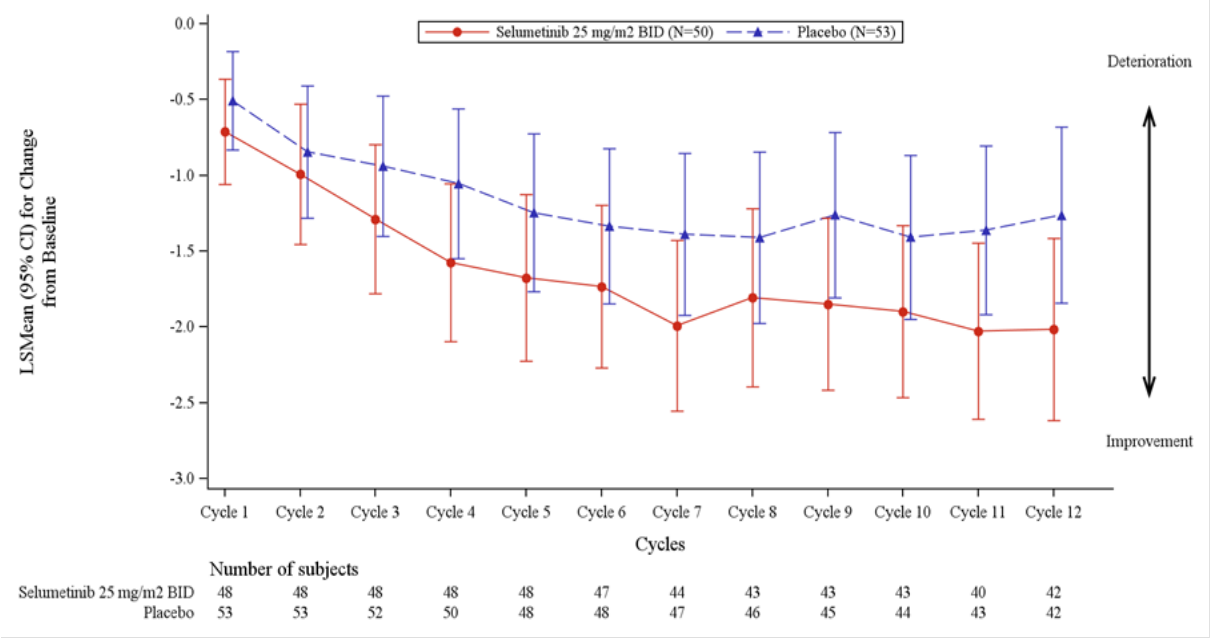
Average PAINS-pNF chronic target PN pain intensity scores for each cycle were derived, regardless of changes in PN pain medication use and target PN surgical resection. Baseline score was derived as average of daily scores during Screening Period, if at least 4 daily pain scores were non-missing in at least 2 non-overlapping 7-day periods. Post-baseline score was derived as average of daily scores within 28-day cycles, if at least 4 daily pain scores were non-missing in at least 3 non-overlapping 7-day periods of the cycle. Daily scores after early crossover and daily scores after prolonged treatment interruption (> 28 continuous days of no study intervention) were excluded.

Table 19: Mean Change From Baseline for PAINS-pNF Chronic Target PN Pain Intensity Score at Cycle 12 (Pain FAS)

Treatment Group	n	LS Mean	SE	95% CI	Comparison of Treatment Groups			
					LS Mean Difference	SE	95% CI	p-value
Selumetinib N = 50	42	-2.0	0.30	(-2.6, -1.4)	-0.8	0.41	(-1.6, 0.1)	0.070
Placebo N = 53	42	-1.3	0.29	(-1.8, -0.7)				

Note: Analysis was based on a MMRM for change from baseline adjusted by treatment group, cycle, baseline score, geographical region, treatment group-by-cycle, baseline score-by-cycle. P-values reflect the 2-sided Type 3 test with alpha = 0.05 level. A negative comparison of treatments favours selumetinib.
Based on DCO date 05 August 2024

Figure 15: LS Mean Change From Baseline in PAINS-pNF Chronic Target PN Pain Intensity Score Over Randomized Period (Pain FAS)



Note: A higher PAINS-pNF score indicates a higher chronic target PN pain intensity. A negative change from baseline indicates an improvement.
Based on DCO date 05 August 2024

Sensitivity Analyses

Sensitivity analyses using multiple imputation techniques of reversion to baseline were performed in the Pain FAS to assess the robustness of the missing at random (MAR) assumptions made for the main analysis of PAINS-pNF chronic target PN pain intensity score regarding missing data following treatment discontinuation any time up to the end of Cycle 12 (discontinuation due to any reason and due to reasons assessed as attributable to treatment) and the treatment policy strategy chosen for the IE of changes in chronic PN pain medication.

A sensitivity analysis was conducted to evaluate the effect of increases in pain medication on the analysis of change from baseline in PAINS-pNF intensity scores and the results were consistent with the main analysis of the key secondary endpoint of PAINS-pNF intensity scores during the Randomized Period.

Impact of Increase in Chronic Pain Medication Use on Chronic Pain Intensity Scores

A higher proportion of participants in the placebo group had an increase in pain medication use compared to the selumetinib group during the Randomised Period in the Pain FAS: 6/50 participants (12.0%, including 2 participants at Cycle 12) and 13/53 participants (24.5%, including 4 participants at Cycle 12), for selumetinib and placebo treatment groups, respectively.

Second key Secondary Endpoint : Plexiform Neurofibroma Quality of Life Scale- Randomized period

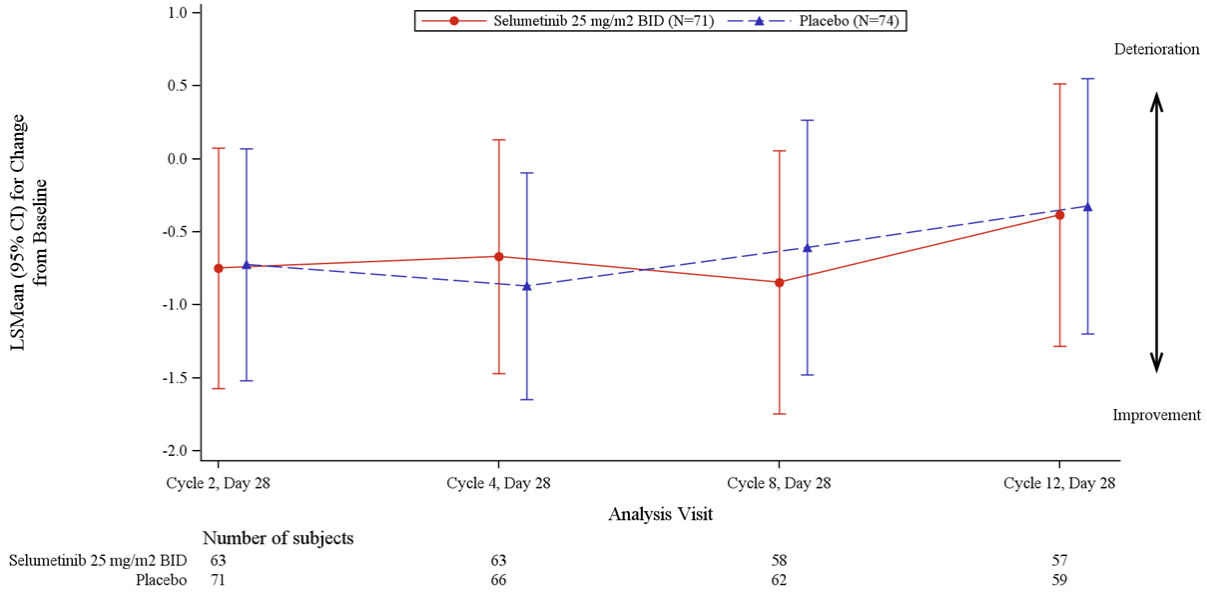
PlexiQoL total scores were derived at each planned site visit while the participant was on treatment until the earliest of treatment discontinuation, early crossover or DCO. Total scores after prolonged treatment interruption (> 28 continuous days of no study intervention) were excluded until recommencement of treatment.

Table 20: Mean Change From Baseline for PlexiQoL Total Score at Cycle 12 (FAS)

Treatment Group	n	estimate	SE	95% CI	Comparison of Treatment Groups			
					LS Mean Difference	SE	95% CI	p-value
Selumetinib N = 71	57	-0.4	0.45	(-1.3, -0.5)	-0.1	0.59	(-1.2, 1.1)	0.918
Placebo N = 74	59	-0.3	0.44	(-1.2, -0.6)				

Note: Analysis was based on a MMRM for change from baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment group-by-cycle, baseline score-by-cycle. Unstructured covariance matrix was used. LS means and LS mean differences were estimated on the treatment group-by-cycle-interaction. P-values were 2-sided Type 3 test with alpha = 0.05. A negative comparison of treatments favours selumetinib.
Based on DCO date 05 August 2024

Figure 16: LS Mean Change From Baseline in PlexiQoL Total Scores Over the Randomized Period (FAS)



Note: Analysis was based on a MMRM for change from baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment group-by-cycle, baseline score-by-cycle. Unstructured covariance matrix was used. LS means on the treatment group cycle interaction were plotted. Error bars represent 95% CIs.

Based on DCO date 05 August 2024

Sensitivity Analyses

Sensitivity analyses using multiple imputation techniques of reversion to baseline were performed to assess the robustness of the MAR assumption made for the main analysis of PlexiQoL total score regarding missing data following treatment discontinuation any time up to the end of Cycle 12 (discontinuation due to any reason and due to reasons assessed as attributable to treatment). The results for both sensitivity analyses were consistent with the main analysis of the PlexiQoL scores in the FAS during the Randomized Period.

Secondary endpoints

Changes in Target PN Volume

Table 21: Percent Change From Baseline in Target PN Volume Over Time Through Cycle 16 (FAS)

Timepoint	Treatment group	N	Actual values (mL)	
			Mean (SD)	Median (min, max)
Baseline	Selumetinib	71	836.27 (2369.340)	110.18 (3.3, 13574.9)
	Placebo	74	539.53 (927.236)	221.85 (9.1, 5261.9)
			% Change from Baseline	
Cycle 4 Day 28	Selumetinib	64	-7.80 (12.736)	-9.88 (-32.7, 28.5)
	Placebo	70	3.29 (9.263)	2.29 (-18.8, 38.6)
Cycle 8 Day 28	Selumetinib	60	-8.83 (15.785)	-10.58 (-41.5, 47.6)
	Placebo	68	2.91 (15.145)	2.19 (-31.0, 71.3)
Cycle 12 Day 28	Selumetinib	57	-9.19 (21.685)	-13.13 (-50.7, 90.3)
	Placebo	63	-0.86 (13.155)	0.00 (-42.2, 28.0)
Cycle 16 Day 28	Selumetinib	52	-13.22 (18.308)	-14.45 (-58.1, 27.6)
	Placebo	61	-8.20 (16.651)	-9.21 (-44.0, 29.5)

Note: Percent change from baseline = (post-baseline value – baseline value) / (baseline value) × 100. A negative change denotes a reduction in target PN volume. Only assessments closest to the study protocol visit day were selected for this summary; therefore, unscheduled visits may have been excluded.

Based on DCO date 05 August 2024

Best Objective Response by Cycle 16

The supplementary analysis of BOR by end of Cycle 16 was based on the same selection of MRI scans as the primary endpoint (i.e., excluded volumetric MRI scans after treatment discontinuation, early crossover, the start of subsequent NF1-PN treatment, progression or prolonged study intervention interruption).

The participants who were not evaluable by the end of Cycle 16 were due to discontinuation of study intervention prior to the first on-treatment MRI scan Day 28 (after crossing over to selumetinib treatment during the Open-label Period)

Table 22: Best Objective Response by End of Cycle 16 – On-treatment MRI Volumetric Assessments Period (FAS)

Best objective response	Selumetinib (N = 71)	Placebo (N = 74)
	n (%)	n (%)
Confirmed CR	0	0
Confirmed PR	14 (19.7)	4 (5.4)
Stable disease	50 (70.4)	63 (85.1)
Unconfirmed CR	0	0
Unconfirmed PR	5 (7.0)	8 (10.8)
Stable disease	45 (63.4)	55 (74.3)
PD	1 (1.4)	5 (6.8)

Best objective response	Selumetinib (N = 71)	Placebo (N = 74)
	n (%)	n (%)
Not evaluable	6 (8.5)	2 (2.7)

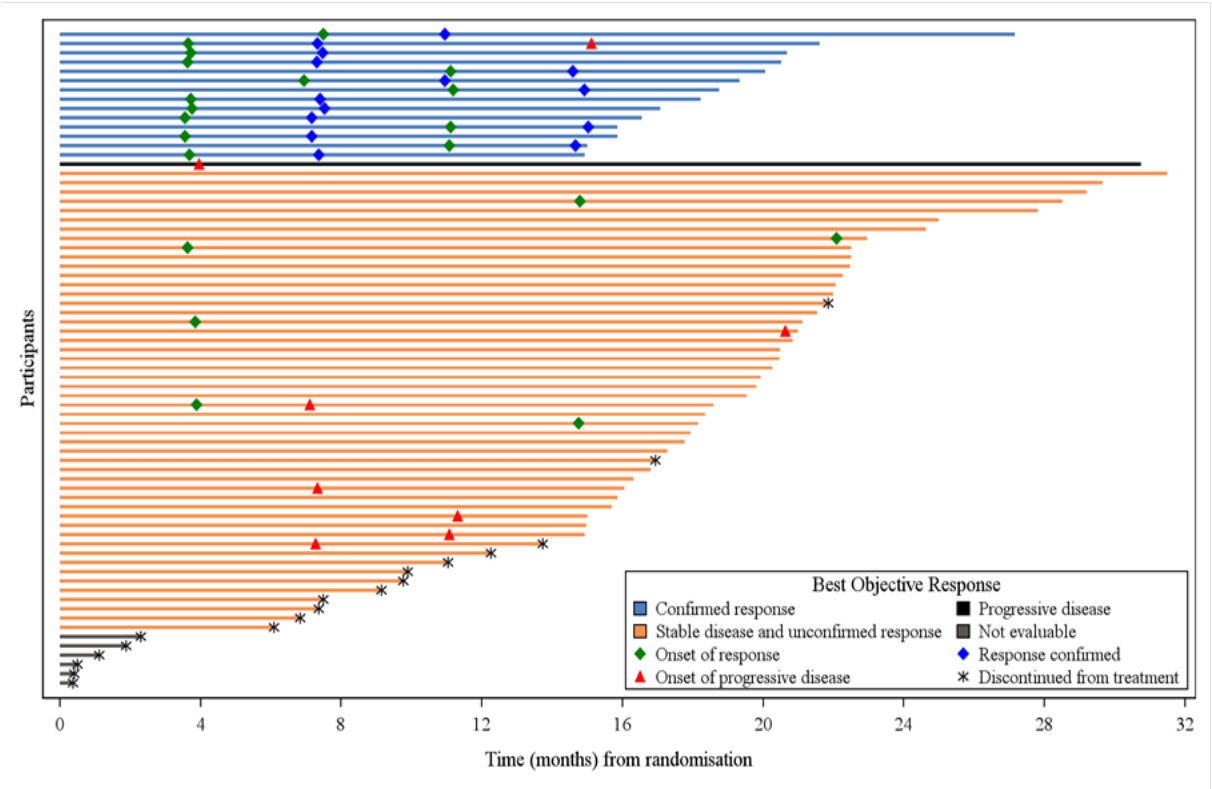
Note: BOR was the best response a participant had following the start of intervention, but prior to starting any subsequent NF1-PN therapy and up to and including progression or the last evaluable MRI assessment in the absence of progression.
Based on DCO date 05 August 2024

Duration of Response As of 05 August 2024 Data Cutoff

As of the DCO date, the median DoR from onset of response had not been reached.

Responses to selumetinib treatment were sustained (per REINS ≥ 6 months DoR); of the 14 participants in the selumetinib group that achieved an objective response, 12 (85.7%) participants remained in response for 6 or more months.

Figure 17: Duration of Response, Swimmer Plot, On-treatment MRI Volumetric Assessments Period – Selumetinib Group (FAS)



Time to Response (Selumetinib Single-arm Analysis)

Table 23: Time to response, primary analysis, on-treatment MRI volumetric assessments period

	Selumetinib 25 mg/m2 BID (N=71)
Number (%) of subjects with a response [a]	14
Median time to response (months) [b]	3.73
95% CI for median time to response [b]	3.61 - 11.07
Response rate at 4 months (%) [b]	42.86
95% CI for response rate at 4 months [b]	17.73 - 66.04
Response rate at 8 months (%) [b]	28.57
95% CI for response rate at 8 months [b]	8.83 - 52.37

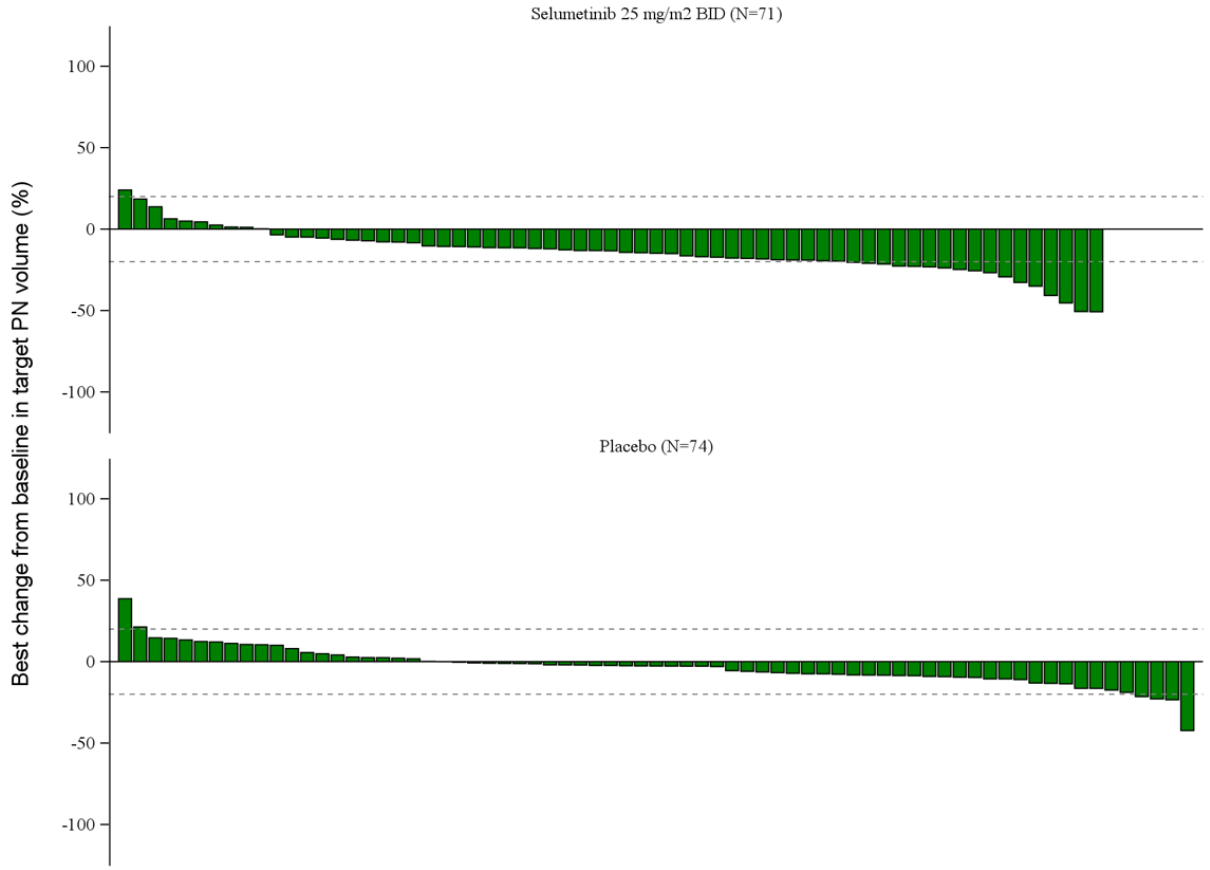
[a] Time to response (TTR) is the time from randomisation date until the date of first documented objective response (which is subsequently confirmed, cCR or cPR) as determined by ICR per REiNS criteria.
[b] Calculated using the Kaplan-Meier technique. Only subjects who have achieved a cCR or a cPR are evaluated for TTR.
Based on DCO date 05 August 2024

Best Percentage Change from Baseline in Target PN Volume – Randomized Period

Following the same approach as the primary analysis, the analysis of the secondary endpoint of the best percentage change from baseline over the randomized period in target PN volume excluded volumetric MRI scans after treatment discontinuation, early crossover, the start of subsequent NF1-PN treatment, progression, or prolonged treatment interruption (> 28 continuous days of no study intervention).

The best percentage change from baseline in target PN volume over the Randomized Period was different in the selumetinib group (LS mean = -15.3%) compared to the placebo group (LS mean = -4.2%) as determined by the difference in mean best percentage change from baseline in target PN volume (LS mean difference = -11.1%; 95% CI: -15.5%, -6.8%; nominal $p < 0.001$) in the FAS.

Figure 18: Target PN Volume, Best Percentage Change During Randomized Period, Waterfall Plot (FAS)



Note: Best percentage change was derived as the maximum reduction from baseline or the minimum increase from baseline in the absence of reduction during the Randomized Period. A negative change denotes a reduction in target PN size. Included all scheduled and unscheduled assessments until the earliest of progression, death, start of subsequent treatment, or the last evaluable MRI assessment.
Based on DCO date 05 August 2024

Chronic Target PN Pain Palliation – Randomized Period

The main definition of chronic target PN Pain palliation was based on pain improvement of ≥ 2 (i.e., reduction ≥ 2) in PAINS-pNF chronic target PN pain intensity score and no increase (≥ 1 in chronic PN pain medication score) in chronic PN pain medication.

Table 24: Chronic Target Pain Palliation at Cycle 12 (Pain FAS)

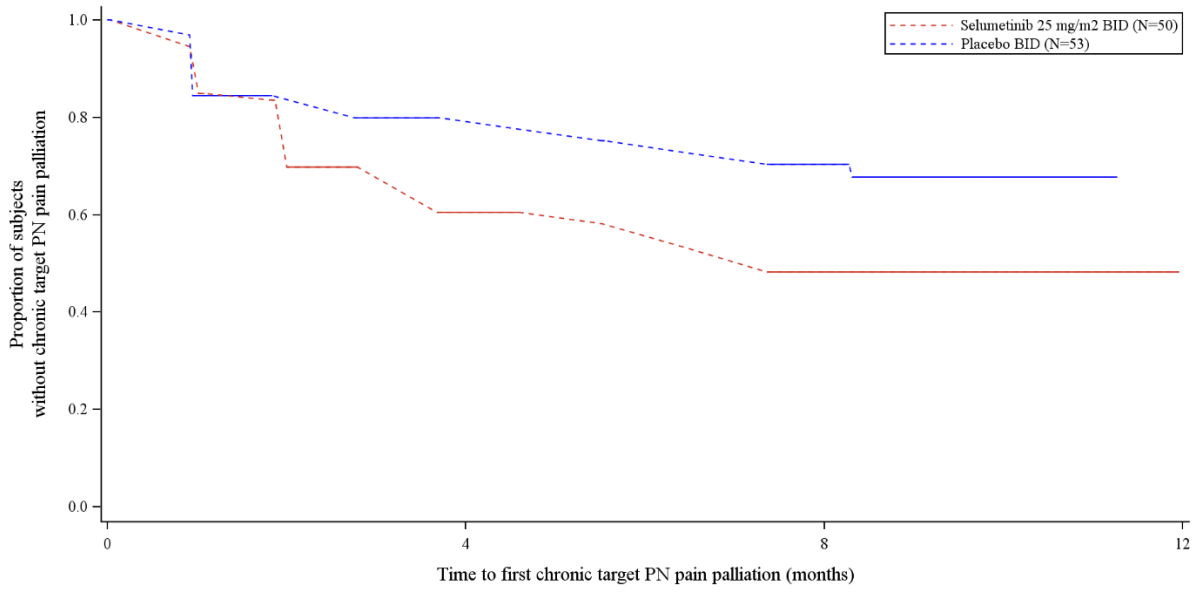
Treatment group	n	Number of responders (%)	Comparison of treatment groups		
			OR	95% CI	p-value
Selumetinib N = 50	41	16 (39.0)	1.5	(0.6, 4.0)	0.405
Placebo N = 53	40	13 (32.5)			

Notes: Chronic target PN pain palliation occurred if an improvement of ≥ 2 in PAINS-pNF chronic target PN pain intensity score and no increase (≥ 1 in chronic PN pain medication score) in chronic PN pain medication were observed. Analysis was based on a generalized linear model for pain palliation adjusted by treatment group, cycle, baseline chronic target PN pain intensity score, baseline chronic PN pain medication modified WHO analgesic ladder score, geographical region, treatment group-by-cycle, baseline intensity score-by-cycle, baseline analgesic score-by-cycle. Each treatment effect and treatment comparisons were estimated by the LS means on the treatment group-by-cycle interaction. P-values were 2-sided with alpha = 0.05. An OR greater than 1 favours selumetinib.

Time to First Chronic Target PN Pain Palliation

Time to first chronic target PN pain palliation during the Randomized Period was numerically shorter, but not statistically significantly different

Figure 19: Time to First Chronic Target PN Pain Palliation During the Randomized Period, Kaplan-Meier Plot (Pain FAS)

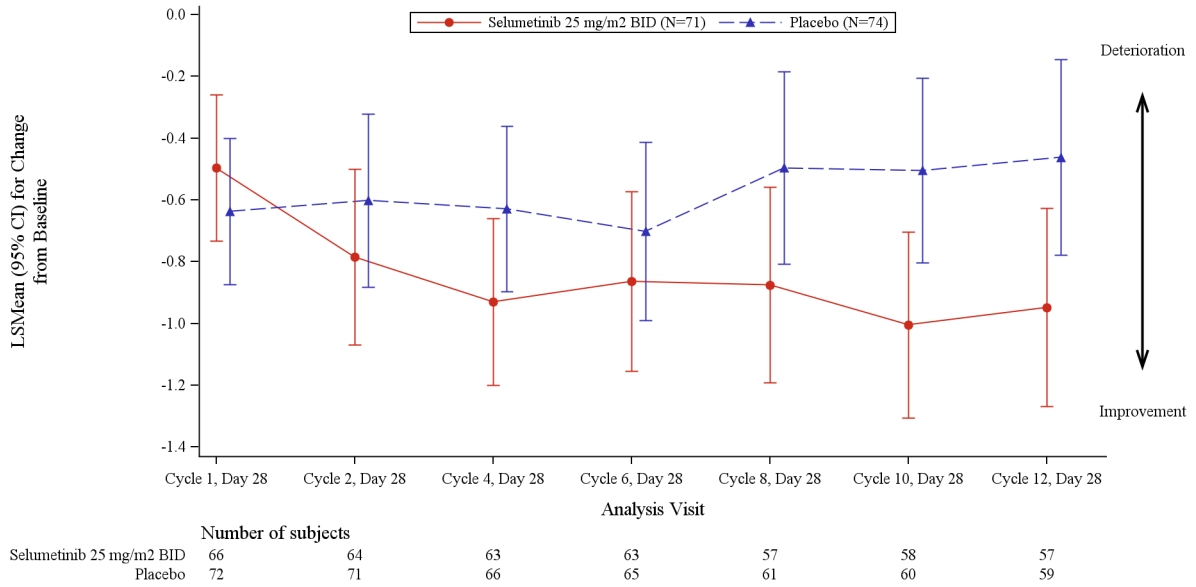


Note: Time to chronic target PN pain palliation was the time from randomization to last day of the first cycle where palliation was achieved. Participants with no palliation were censored at last day of the Randomized Period.
Based on DCO date 05 August 2024

PII-pNF Pain Interference Total Score – Randomized Period

At Cycle 12, there was a nominally statistically significant difference in PII-pNF pain interference total score in the) between the selumetinib group (LS mean = -0.9; 95% CI = -1.3, -0.6) and the placebo group (LS mean = -0.5; 95% CI = -0.8, -0.1).

Figure 20: LS Mean Change From Baseline in PII-pNF Pain Interference Total Scores Over the Randomized Period (FAS)

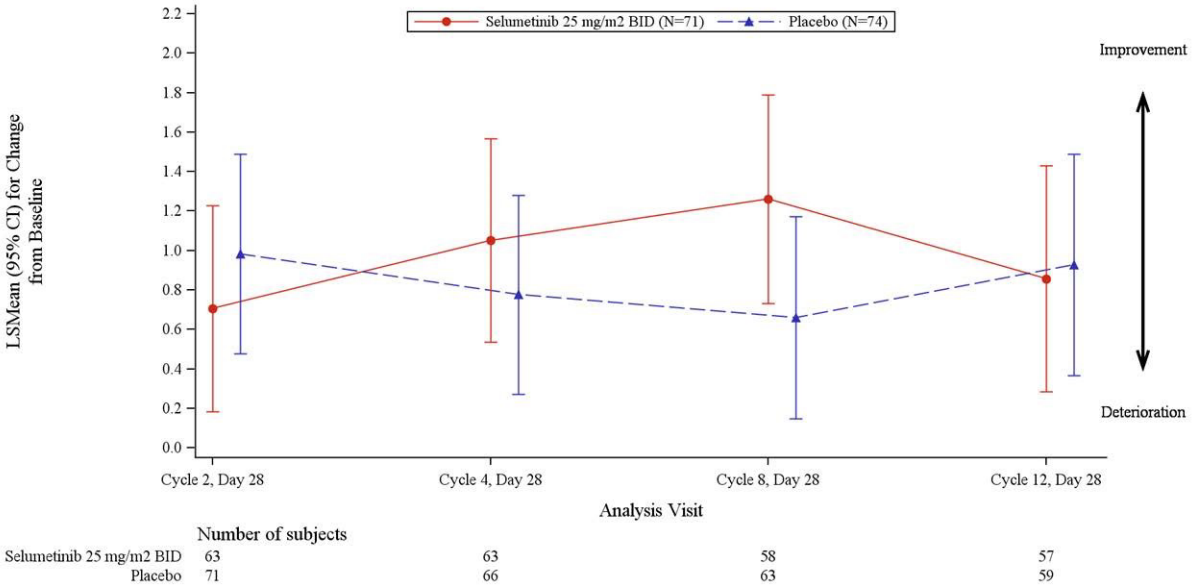


Note: Analysis was based on a MMRM for change from baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment group-by-cycle, baseline score-by-cycle. Unstructured covariance matrix was used. LS means on the treatment group-by-cycle interaction were plotted. Error bars represent 95% CIs.
Based on DCO date 05 August 2024

PROMIS Physical Function – Randomized Period

At the end of Cycle 12, there was no statistically significant difference in PROMIS Physical Function total scores (LS mean difference = -0.1; 95% CI: -0.8, 0.7; nominal p = 0.850) between the selumetinib group (LS mean = 0.9; 95% CI: 0.3, 1.4) and the placebo group (LS mean = 0.9; 95% CI: 0.4, 1.5)

Figure 21: LS Mean Change from Baseline in PROMIS Physical Function Total Score Over the Randomized Period (FAS)

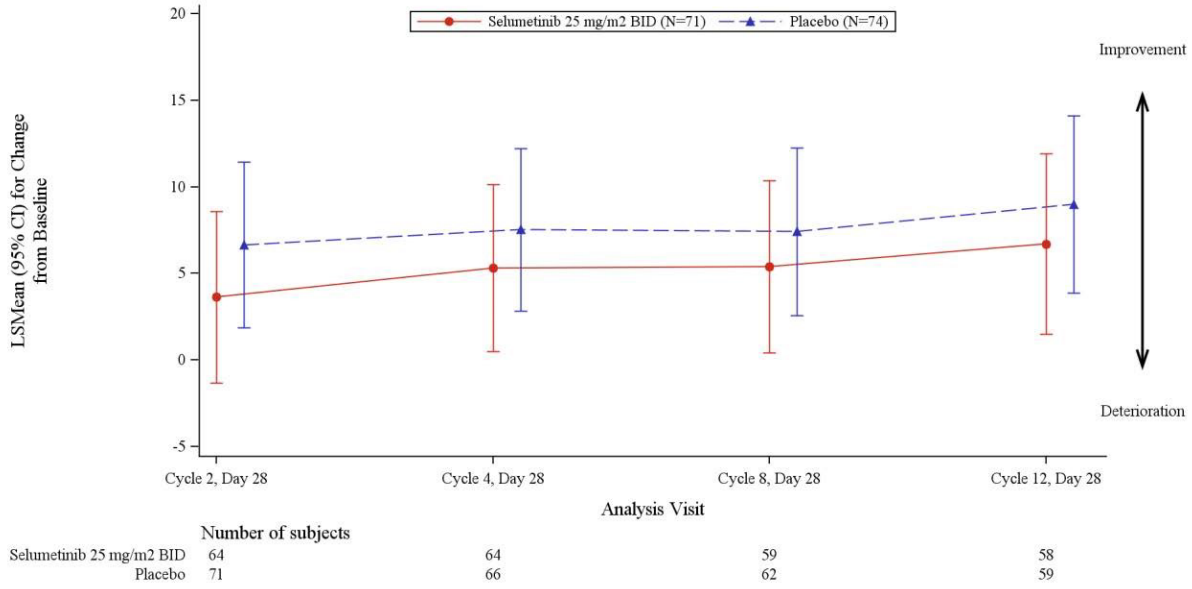


Note: Analysis was based on a MMRM for change from baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment group-by-cycle, baseline score-by-cycle. Unstructured covariance matrix was used. LS Means on the treatment group-by-cycle interaction were plotted. Error bars represent 95% CIs.

PedsQL (NF1 module acute Version 3.0 – adult report) – randomised period

In the FAS, both treatment groups showed numerically higher scores through Cycle 12 compared to baseline, the mean change from baseline in the PedsQL skin sensations scores at Cycle 12 Day 28 showed no nominally statistically significant difference in the selumetinib group (LS mean = 6.7; 95% CI: 1.5, 11.9) compared to the placebo group (LS mean = 9.0; 95% CI: 3.9, 14.1) as determined by the difference in mean change (LS mean difference = -2.2; 95% CI = -8.8, 4.3; nominal p-value = 0.500).

Table 25: LS Mean Change From Baseline in PedsQL Skin Sensations Scores During the Randomized Period (FAS)

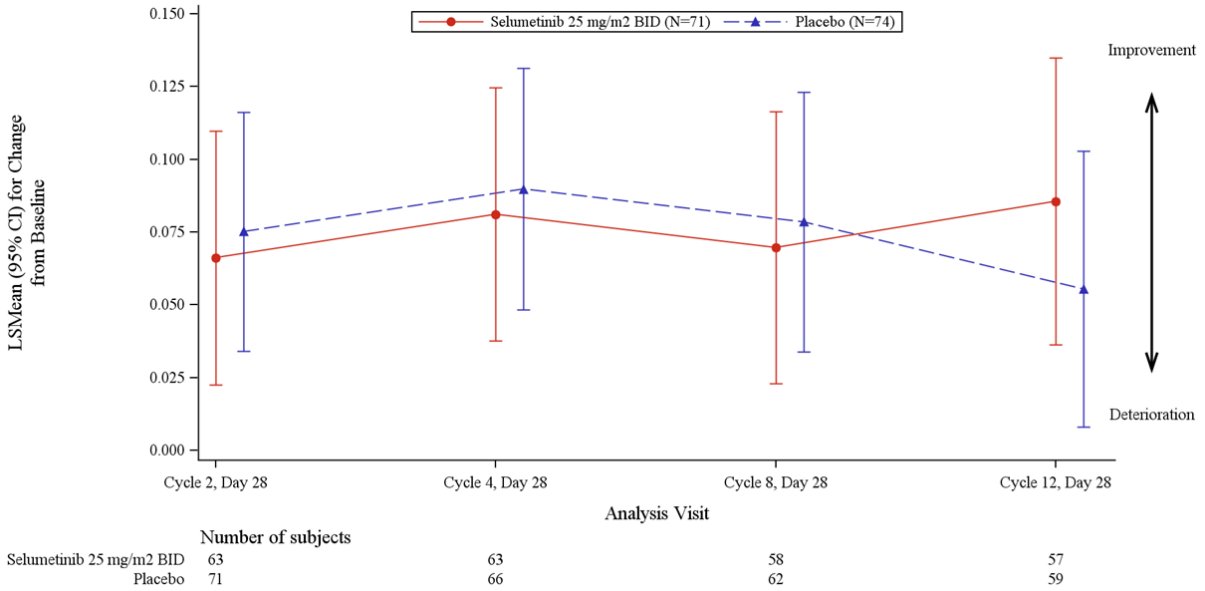


Note: Analysis was based on a MMRM for Change from Baseline adjusted by pain intensity group, treatment group-by-cycle, baseline score, geographical region, treatment group-by-cycle, baseline score-by-cycle. Unstructured covariance matrix was used. LS means on the treatment group-by-cycle interaction were plotted. Error bars represent 95% CIs.
Based on DCO date 05 August 2024

EQ-5D-5L – Randomized Period

During the Randomized Period, numerically higher scores were observed in both treatment groups compared to baseline. At Cycle 12 Day 28, the LS mean change from baseline in the EQ-5D-5L index score was 0.09 (95% CI: 0.04, 0.13) in the selumetinib group and was 0.06 (95% CI: 0.01, 0.10) in the placebo group; the LS mean difference was 0.03 (95% CI = -0.03, 0.09; nominal p = 0.335).

Figure 22: LS Mean Change From Baseline in EQ-5D Index Score Over the Randomized Period (FAS)



Note: Analysis was based on MMRM for change from baseline adjusted by pain intensity group, treatment group, cycle, baseline score, geographical region, treatment group-by-cycle, and baseline score-by-cycle. Unstructured covariance matrix was used. LS means on the treatment group-by-cycle interaction were plotted. Error bars represent 95% CIs.
Based on DCO date 05 August 2024

Updated efficacy results from final DCO

During the procedure, , the MAH provided data based on the Final DCO (when the last participant had the opportunity to reach Cycle 24 Day 28 visit) that occurred on 17 March 2025, approximately 8 months after the Primary Analysis (DCO2, 05 August 2024) which was initially submitted for this variation. At the Final Analysis, the median total exposure was approximately 2 years (compared with approximately 1.5 years at the Primary Analysis).

Table 26: Duration of exposure, on-selumetinib period (On-selumetinib safety analysis set)

Characteristic	Statistic	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Total exposure (days) [a]	n	71	66	137
	Mean	675.1	462.0	572.4
	SD	300.78	192.46	275.12
	Min	11	10	10
	Q1	515.0	344.0	372.0
	Median	749.0	475.5	566.0
	Q3	862.0	566.0	789.0
	Max	1182	844	1182
	Total treatment days	47932	30491	78423
Total exposure periods, n (%) [a]				
n	n (%)	71 (100)	66 (100)	137 (100)
< 12 months	n (%)	14 (19.7)	20 (30.3)	34 (24.8)
>= 12 - <= 24 months	n (%)	19 (26.8)	38 (57.6)	57 (41.6)
> 24 - <= 36 months	n (%)	35 (49.3)	8 (12.1)	43 (31.4)
> 36 months	n (%)	3 (4.2)	0	3 (2.2)

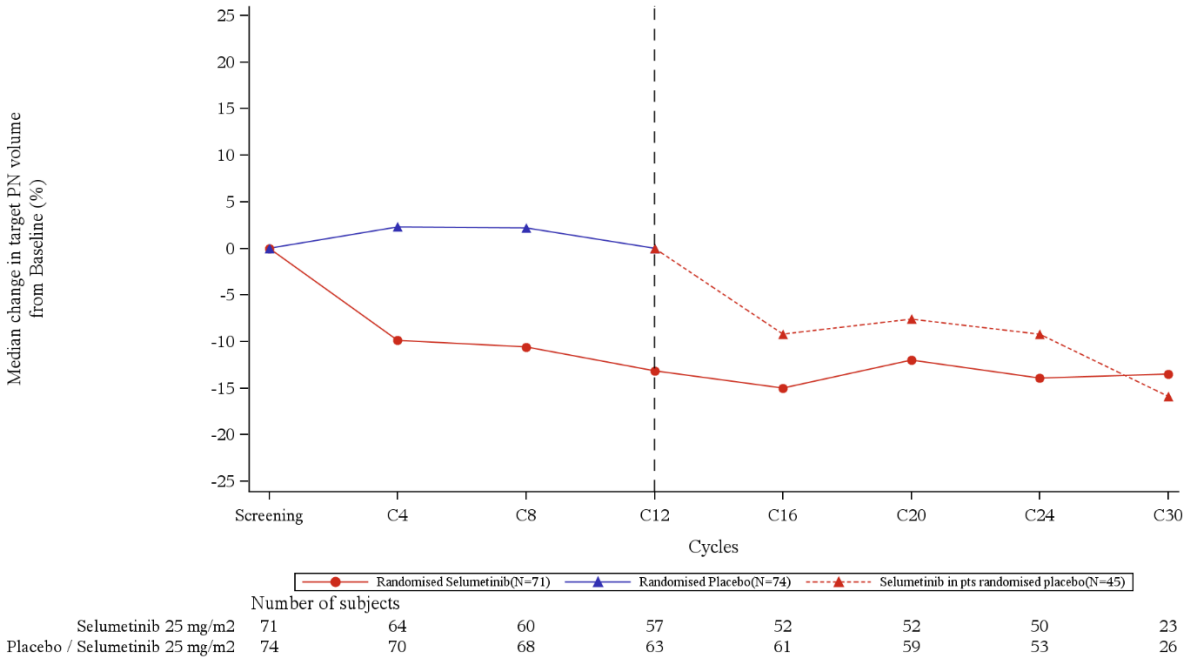
[a] Total exposure = last selumetinib dose date - first selumetinib dose date + 1.

In the 14 participants who had a confirmed response at the time of the Primary Analysis, all had a response ≥ 6 months and 9 (64.3%) participants remained in response for ≥12 months at Final Analysis, compared to 68.2% and 21.4%, respectively, at the Primary Analysis.

Percentage change from baseline in target PN volume

In the selumetinib group of the FAS, the median (min, max) best percentage change from baseline observed was -15.75% (-59.0%, 23.0%) at the time of the Primary Analysis and -16.91% (-59.0%, 23.0%) at the time of the Final Analysis. In the placebo/selumetinib group (placebo participants switching to selumetinib), a decreasing median percentage change from baseline in target PN volume was observed from Cycle 12 onwards

Figure: 23: Median Percent Change from Baseline in Target PN Volume (mL) Over Study (FAS)



Placebo participants are planned to cross over to selumetinib at the end of Cycle 12 (vertical dash black line).
Based on DCO date 17 March 2025

Duration of response

Table 27: Duration of response in primary endpoint responders, primary analysis, on-treatment MRI volumetric assessments period (Selumetinib full analysis set)

	Selumetinib 25 mg/m2 BID (N=71)
Subjects with objective response	14
Number of responders who subsequently progressed or died	3
Duration of response from onset of response (months) [a] [b]	
25th percentile	18.4
Median	NC
95% CI for median duration of response	11.50 - NC
75th percentile	NC
Number and percentage remaining in response n (%)	
>= 6 months	14 (100)
>= 8 months	14 (100)
>= 12 months	9 (64.3)
>= 16 months	8 (57.1)
>= 20 months	3 (21.4)
>= 24 months	1 (7.1)

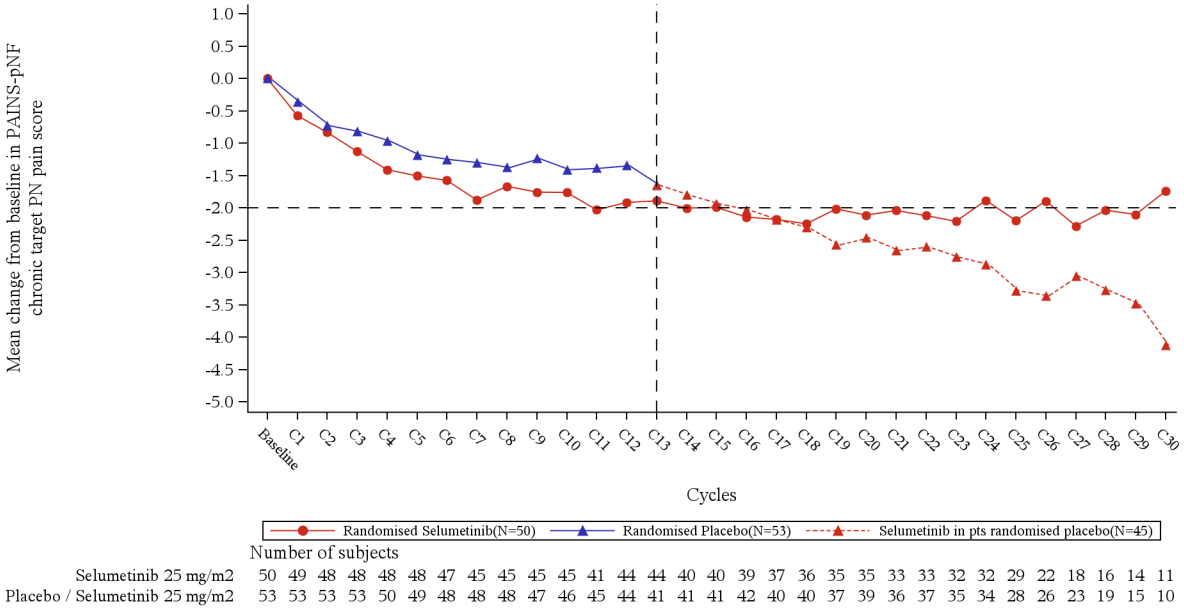
[a] Duration of response (DoR) is the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression as assessed by ICR per REiNS criteria or death due to any cause, or last evaluable MRI assessment for subjects that do not progress. For subjects that progress after two or more consecutive missed MRI assessments, the subject is censored at the time of the latest evaluable MRI assessment prior to the missed visits.

[b] Calculated using the Kaplan-Meier technique. Only includes subjects who have a confirmed complete response or a confirmed partial response prior to the end of cycle 16, as of DCO 05Aug2024.

Pain

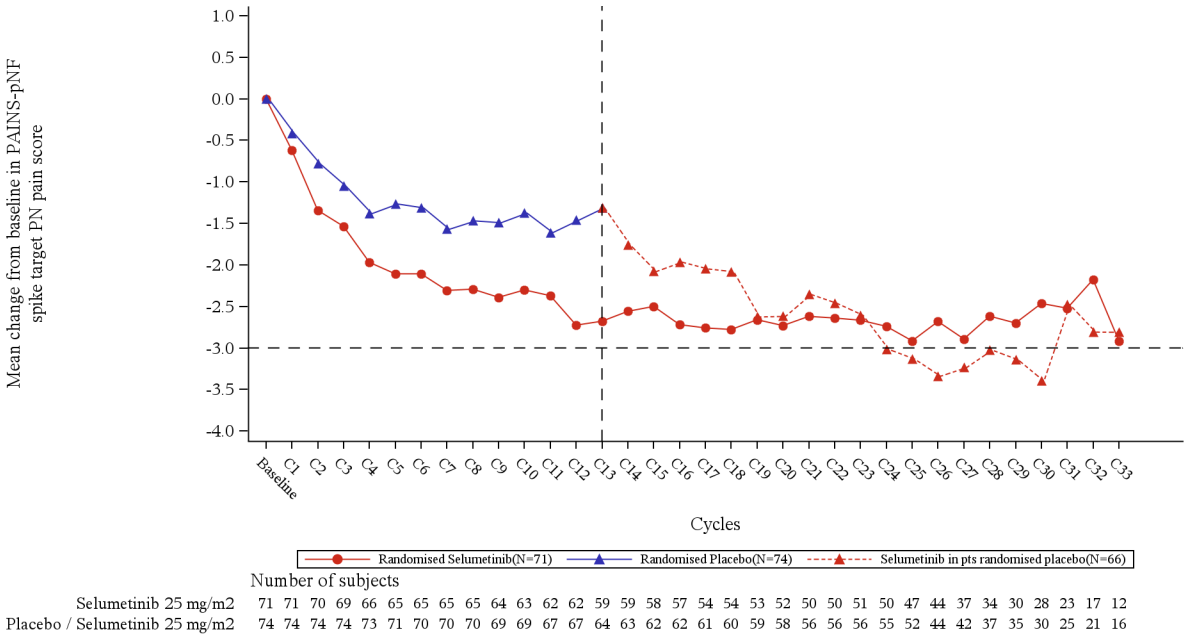
Results of the Final Analysis in pain-related endpoints are shown in Figure 24 for PAINS-pNF chronic target PN pain intensity score, Figure 25 for PAINS-pNF spike target PN pain intensity score, Figure 26 for PII-pNF pain interference total score, and Figure 27 for participants with decreases in pain medication as reported in the e-Diary.

Figure 24: Mean Change from Baseline in PAINS-pNF Chronic Target PN Pain Intensity Scores Over Study (Pain FAS)



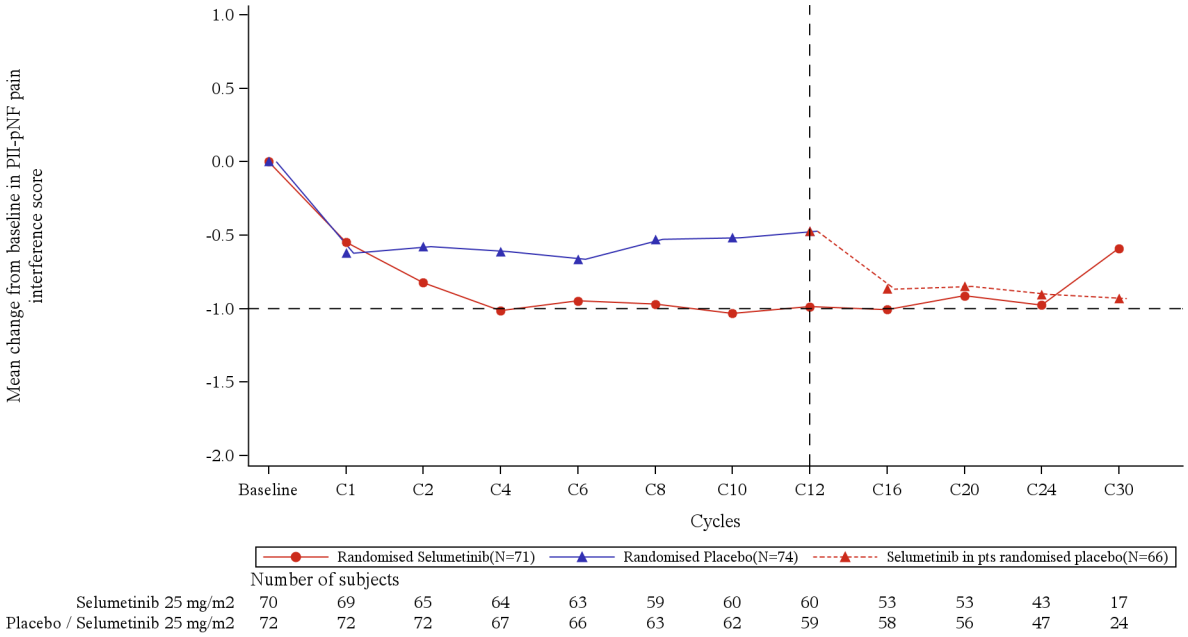
Cycles where data from less than 10 participants in a treatment group are available are omitted from the figure. Placebo participants are planned to cross over to selumetinib at the end of Cycle 12 (vertical dash black line). MSD for change from baseline in = -2.0 (horizontal black dash line).
Based on DCO date 17 March 2025

Figure 25: Mean Change from Baseline in PAINS-pNF Spike Target PN Pain Intensity Score Over Study (FAS)



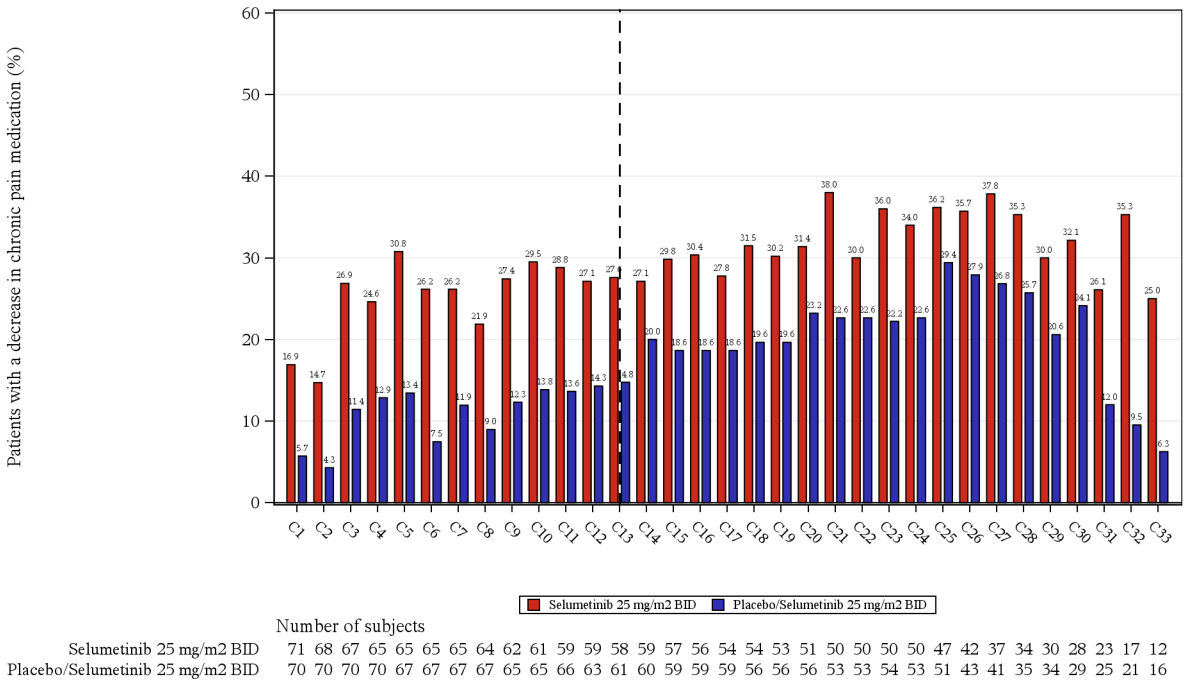
Cycles where data from less than 10 participants in a treatment group are available are omitted from the figure. Placebo participants are planned to cross over to selumetinib at the end of Cycle 12 (vertical dash black line). MSD for change from baseline in = -3.0 (horizontal black dash line).
Based on DCO date 17 March 2025

Figure 26: Mean Change from Baseline in PII-pNF Pain Interference Total Score Over Study (FAS)



Cycles where data from less than 10 participants in a treatment group are available are omitted from the figure. Placebo participants are planned to cross over to selumetinib at the end of Cycle 12 (vertical dash black line). MSD for change from baseline in PII-pNF = -1.0 (horizontal black dash line).
Based on DCO date 17 March 2025

Figure 27: Pain Medication Decrease as Reported in the e-Diary Over Study (FAS)



Number of subjects

	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	C15	C16	C17	C18	C19	C20	C21	C22	C23	C24	C25	C26	C27	C28	C29	C30	C31	C32	C33
Selumetinib 25 mg/m2 BID	71	68	67	65	65	65	65	64	62	61	59	59	58	59	57	56	54	54	53	51	50	50	50	50	47	42	37	34	30	28	23	17	12
Placebo/Selumetinib 25 mg/m2 BID	70	70	70	70	67	67	67	67	65	65	66	63	61	60	59	59	59	56	56	56	53	53	54	53	51	43	41	35	34	29	25	21	16

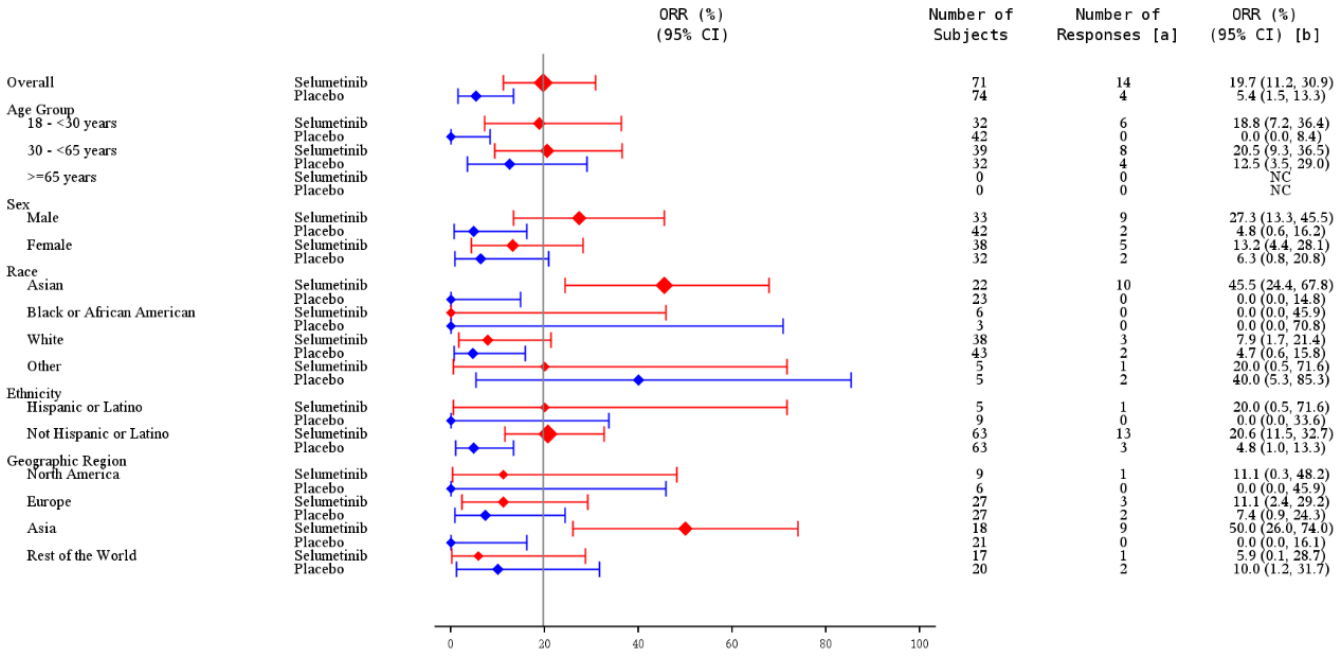
Cycles where data from less than 10 participants in a treatment group are available are omitted from the figure.
Placebo participants are planned to cross over to selumetinib at the end of Cycle 12 (vertical dash black line).
Based on DCO date 17 March 2025

Ancillary analyses

Subgroups analysis of Objective Response Rate

The ORR by the end of Cycle 16 of each treatment group is summarized by subgroup (age, sex, race, ethnicity, and geographic region) in Figure 28.

Figure 28: Forest Plot of Objective Response Rate by End of Cycle 16, Primary Analysis, On-Treatment MRI Volumetric Assessments Period by Subgroup (FAS)



[a] Includes participants with a confirmed CR or cPR as determined by ICR as per the REiNS criteria.

[b] 2-sided exact 95% CI calculated using the Clopper-Pearson method.

Note: Diamond denotes the point estimate and size are proportional to the number of responses.

FAS - participants randomized to study intervention. On-treatment MRI volumetric assessment period -from first dose until discontinuation or DCO (whichever occurs first), excluding data during prolonged study intervention interruption (> 28 continuous days of no study intervention) or within 28 days of recommencement.

Based on DCO date 05 August 2024.

Summary of main study

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28: Summary of Efficacy for trial KOMET

Title: A Phase III, Multicentre, International Study with a Parallel, Randomized, Double-blind, Placebo-controlled, Two-arm Design to Assess the Efficacy and Safety of Selumetinib in Adult Participants with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET)		
Study identifier	D134BC00001	
Design	Randomized, double-blind, parallel-group, multicenter international Phase III study	
	Duration of main phase:	Twelve 28-day cycles
	Duration of Extension phase:	Twelve additional 28-day cycles
Hypothesis	Superiority of selumetinib versus placebo	

Treatments groups	Selumetinib		25 mg/m2 bid based on BSA dosing 71 participants were randomized and received at least 1 dose of study intervention Twelve 28-day cycles for the randomized period
	Placebo		Twelve 28-days cycles 74 participants were randomized and received at least 1 dose of study intervention
Endpoints and definitions	Primary endpoint	ORR	Overall response rate at the end of cycle 16 Using volumetric MRI analysis as determined by ICR (per REiNS criteria)
	Key Secondary	PAINS-pNFc	Difference of the means in the change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib and placebo amongst participants with a PAINS-pNF chronic target PN pain intensity score ≥ 3 at baseline,
	Key Secondary	PlexiQoL	Difference in change from baseline in PlexiQoL total score between selumetinib and placebo at Cycle 12 amongst participants with a PlexiQoL total score at baseline and at least one post-baseline total score.
	Secondary endpoints		• Best Percentage Change from Baseline in Target PN Volume • Chronic Target PN Pain Palliation • Chronic PN Pain Medication Use • PII-pNF Pain Interference Total Score • PROMIS Physical Function • PedsQL NF1 • EQ-5D-5L • EQ-VAS
Database lock	Data cutoff: 05 August 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The primary objective was the proportion of participants who have confirmed partial and complete response rate (ORR) by end of Cycle 16 using volumetric MRI analysis as determined by ICR (per REiNS criteria). Full analysis set (All participants who were randomized to study intervention in the study.)		
Descriptive statistics and estimate variability	Treatment group	selumetinib	Placebo
	Number of subjects	71	74
	Response rate n (%)	14 (19.7)	4 (5.4)
	95% CI	(11.2, 30.9)	(1.5, 13.3)
Effect estimate per comparison	Difference in response rate (%) based on Full analysis set	Selumetinib vs placebo	
		Difference between selumetinib and placebo (%)	14.3
		95% IC	3.8, 25.8
		P-value	0.012
Notes			

Analysis description	Key Secondary analysis		
	Mean Change From Baseline for PAINS-pNF Chronic Target PN Pain Intensity Score at Cycle 12 (Pain FAS)		
Descriptive statistics and estimate variability	Treatment group	selumetinib	Placebo
	Number of subjects	42	42
	LS mean PAINS-pNF chronic target PN pain intensity scores	-2.0	-1.3
	SE	0.30	0.29
	95% CI	(-2.6, -1.4)	(-1.8, -0.7)
Effect estimate per comparison	Difference in LS mean PAINS-pNF chronic target PN pain intensity	Selumetinib vs placebo	
		LS Mean Difference	-0.8
		SE	0.41
		95% CI	-1.6, 0.1
		P-value	0.070
	Mean Change From Baseline for PlexiQoL Total Score at Cycle 12 (FAS)		
Descriptive statistics and estimate variability	Treatment group	selumetinib	Placebo
	Number of subjects	57	59
	Mean Change From Baseline	-0.4	-0.3
	SE	0.45	0.44
	95% CI	(-1.3, 0.5)	(-1.2, 0.6)
Effect estimate per comparison	Difference in Mean Change From Baseline	Selumetinib vs placebo	
		LS Mean Difference	-0.1
		SE	0.59
		95% CI	-1.2, 1.1
		P-value	0.918

Clinical studies in special populations

Elderly population

The safety and efficacy of Koselugo in adults with NF1-PN older than 65 years of age has not been established. No data are currently available in NF1-PN patients 65 years of age and older.

Supportive study

Study 11

Design

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

The adult cohort: included Chinese patients ≥18 years of age at the time of study enrolment diagnosed with (i) NF1 per NIH Consensus Development Conference Statement 1988 and (ii) inoperable PN. In addition to PN, patients must have at least 1 other diagnostic criterion for NF1 (NIH Consensus Development Conference Statement 1988).

Objectives

Primary objective:	**Endpoints**
To assess the safety and tolerability of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN	Paediatric and adult cohorts: Safety and tolerability were to be evaluated in terms of AEs, clinical safety laboratory assessments, physical examination, vital signs, height/weight, ECG, echocardiogram, ophthalmologic assessment and performance status
To characterise the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Chinese paediatric and adult patients with NF1 and inoperable PN.	PK parameters for selumetinib and N-desmethyl selumetinib were to be derived from following single dose and multiple doses.
Secondary objectives:	**Endpoints**
To evaluate the clinical efficacy of selumetinib in Chinese paediatric and adult patients with NF1 and inoperable PN on ORR, DoR, PFS, TTP, and TTR	ORR was defined as the proportion of patients who had a complete response or confirmed partial response (defined as a target PN volume decrease ≥20% compared to baseline, confirmed by a consecutive scan within 3 to 6 months after first response), as determined by the investigator and independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. DoR was defined as the time from the date of first documented response (which was subsequently confirmed) until the date of documented progression or death in the absence of disease progression, as determined by the investigator and independent central review per REiNS criteria. PFS was defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review, or death due to any cause. TTP was defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review. TTR was defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed), as determined by the investigator and independent central review per REiNS criteria.
To evaluate the effect of selumetinib on pain in Chinese paediatric and adult patients with NF1 and inoperable PN	FLACC scale (3 years of age). Faces pain scale - revised (4 to 17 years of age). NRS-11 (adult cohort). PII (adult cohort; self- and parent reported in the paediatric cohort).

	Pain Medication Survey (self-reported in the adult cohort; parent-reported in the paediatric cohort).
To determine the effect of selumetinib on HRQoL	PedsQL (paediatric cohort; self- and parent-reported). EORTC QLQ-C30 and PlexiQoL (adult cohort)
To determine the effect of selumetinib on physical functioning	PROMIS (upper extremity; self- and parent-reported in the paediatric cohort). PROMIS (mobility; self- and parent reported in the paediatric cohort). PROMIS Physical Function - Short Form 8c 7-day (adult cohort).

Statistical Methods

There was no formal hypothesis testing performed in Study 11.

Efficacy tumour-related endpoints, including ORR, target PN volume change, TTR, DoR, TTP, and PFS, were presented based on investigator and ICR assessment per REiNS criteria. ORR was presented with corresponding 2-sided exact 95% CI based on the Clopper-Pearson method. Kaplan-Meier (KM) plots of DoR, PFS, TTR, and TTP were presented, and the median DoR, PFS, TTR, and TTP, along with 95% CI, were calculated using the KM method.

Descriptive statistics were provided for Best Objective Response (BOR). Changes in PN growth were evaluated descriptively by summarizing percentage and absolute changes in PN volume from baseline.

The effects of selumetinib on pain were evaluated using the NRS-11 and the PII for the adult cohort. The effects on health-related quality of life (HRQoL) were evaluated using the PlexiQoL scale for the adult cohort. The primary analysis of these outcomes was based on descriptive statistics. Additionally, change from baseline was analysed using an MMRM approach, with baseline score and scheduled visit included in the model as fixed factors.

Baseline data

Adult Cohort

Table 29: Demographic characteristics

Demographic characteristic	**Adult (N = 16)**	
Age (years)	n	16
	Mean	26.1
	SD	8.55
	Median	24.5
	Min	18
	Max	51
Sex n (%)	Male	9 (56.3)
	Female	7 (43.8)
Race n (%)	Asian	16 (100)
	Total	16 (100)

Ethnic group n (%)	Not Hispanic or Latino	16 (100)
	Total	16 (100)
Ethnic population n (%)	Chinese	16 (100)

Efficacy results

Objective Response Rate

The ORR based on investigator assessment was 37.5% (6 out of 16 patients; 95% CI: 15.2%, 64.6%).

Based on ICR assessment, the ORR was 31.3% (5/16 patients; 95% CI: 11.0%, 58.7%).

Table 30: **Best Overall Response of Adult Cohort, Based on Investigator/ICR Assessments According to REiNS (Safety Analysis Set)**

	Number (%) of participants (N = 16)	
	Investigator assessment	**ICR assessment**
BOR		
CR	0	0
cPR [a]	6 (37.5)	5 (31.3)
Unconfirmed PR [b]	5 (31.3)	3 (18.8)
Stable disease [c]	5 (31.3)	7 (43.8)
REiNS progression [d]	0	1 (6.3) [e]
Not evaluable	0	0
ORR [f]	6 (37.5)	5 (31.3)
95% CI [g]	15.2, 64.6	11.0, 58.7

a PR is a decrease in volume of the target PN by 20% or more compared to baseline, and a response of non-PD in the non-target PN, and no new lesions. It is considered unconfirmed at the first detection, confirmed when observed again within 3 to 6 months.
b PR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.
c Insufficient volume change in either target or non-target PN from baseline to qualify for either PR or PD, and no new lesions observed.
d At least one of: Increase in the volume of the target PN by 20% or more compared to baseline or the time of best response (maximal tumour shrinkage) after documenting a PR; increase in the volume of the non-target PN by 20% or more compared to baseline; appearance of a new PN.
e One patient had a haematoma noted in the target lesion at an unscheduled visit near Cycle 4, and the response at this unscheduled visit was PD by ICR. However, the following assessments for Cycle 4 and Cycle 12 were both SD.
f Includes patients with a CR or cPR as determined by investigator/ICR per the REiNS criteria.
g 2-sided exact 95% CI calculated using the Clopper-Pearson method
Note: Based on DCO 15 August 2023.

TTR and DoR

TTR and DoR analysis included patients who reached CR or cPR as of this DCO (15 August 2023).

As of this DCO, based on investigator assessment, 6 patients (37.5%) achieved cPR, the median TTR was 3.9 (95% CI: 3.55, NC) months, and the median DoR was not reached. 5 patients were still in response at the DCO, 3 patients had discontinued treatment. The shortest DoR was 4.1 months, and the longest DoR was 24.1 months.

As of this DCO, based on ICR assessment, 5 patients (31.3%) achieved cPR, the median TTR was 7.9 (95% CI: 3.81, NC) months, and the median DoR was not reached. 3 patients were still in response at the DCO. The shortest DoR was 3.7 months, and the longest DoR was 20.2 months.

Progression-free Survival

As of this DCO, based on investigator assessment, no patient had PD, and the median PFS was not reached. The investigator-assessed PFS rate at 24 cycles was 100%. Based on ICR assessment, 6 patients (37.5%) had PD, and the median PFS was not reached. The median (range) follow-up time was 22.31 months (3.6 to 27.8). The ICR-assessed PFS rate at 24 cycles was 67.0% (95% CI: 37.87, 84.74).

Pain Assessment

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

Table 31: Pain Scale Scores and Changes from Baseline Over Time of Adult Cohort (Safety Analysis Set)

Questionnaire (N = 16)	Time point	Result						Change from baseline					
		n	Mean	SDev	Median	Min	Max	n	Mean	SDev	Median	Min	Max
NRS-11 Physician selected target tumour pain	Baseline	16	1.1	1.53	0.5	0	5	16					
	Cycle 4, Day 28	15	1.1	1.58	0.0	0	5	15	-0.1	1.39	0.0	-3	2
	Cycle 8, Day 28	15	0.9	1.67	0.0	0	6	15	-0.2	1.86	0.0	-3	4
	Cycle 24, Day 28	13	1.3	1.89	0.0	0	5	13	0.1	1.93	0.0	-4	3
NRS-11 Overall tumour pain	Baseline	6	2.2	2.14	1.5	0	6	6					
	Cycle 4, Day 28	6	2.3	2.42	2.0	0	6	5	0.8	1.64	0.0	-1	3
	Cycle 8, Day 28	6	2.8	3.06	2.0	0	7	5	0.8	2.49	0.0	-1	5
	Cycle 24, Day 28	6	3.3	2.07	4.0	0	6	5	1.4	2.51	1.0	-2	5
NRS-11 Overall pain	Baseline	5	2.2	1.92	2.0	0	5	5					
	Cycle 4, Day 28	5	3.0	2.00	2.0	1	6	1	-1.0	NC	-1.0	-1	-1
	Cycle 8, Day 28	3	3.7	2.52	4.0	1	6	0	NC	NC	NC	NC	NC
	Cycle 24, Day 28	5	2.6	1.95	2.0	0	5	1	-1.0	NC	-1.0	-1	-1
PII self-report total score	Baseline	16	1.50	1.638	1.08	0.0	5.3	16					
	Cycle 4, Day 28	15	1.17	1.885	0.00	0.0	5.5	15	-0.43	0.675	-0.33	-1.5	1.0
	Cycle 8, Day 28	15	1.31	2.012	0.50	0.0	6.0	15	-0.29	0.853	0.00	-2.0	1.5
	Cycle 24, Day 28	13	1.18	1.380	0.50	0.0	3.7	13	-0.21	0.711	-0.17	-1.7	1.0

The adult cohort completed NRS-11 and self-reported PII. NRS-11 scale is scored from 0 to 10, with 0 representing no pain and 10 representing 'worst pain you can imagine'.
Response to overall tumour pain was only required by patients reporting multiple tumour pain locations.
Response to overall pain was only required by patients reporting other kinds of pain.
The post-baseline assessment closest to the scheduled visit date (calculated from day of first dosing) is summarised.
Only time points with at least one completed form are included.
The total PII score is the mean of the completed items, scored on a scale of 0 to 6 where a higher score indicates more interferences on daily activities. The total PII score is only computed if at least 4 of the 6 items are answered.
Note: Based on DCO 15 August 2023.

2.6.3. Discussion on clinical efficacy

The application is mainly based on an ongoing phase III, randomized, double-blind, parallel-group, multicenter international study to evaluate the safety, efficacy, and PK of selumetinib administered orally compared to placebo in adult participants with NF1 who have symptomatic, inoperable plexiform neurofibromas (KOMET).

Supportive efficacy data come from the adult cohort of Study D1346C00011 (Study 11) an open label Phase I study that aimed to assess the safety, tolerability, PK, and clinical efficacy of selumetinib in adults and paediatrics Chinese participants with NF1 and inoperable PN. The primary objectives were safety, tolerability and PK, and efficacy was a secondary objective. This study (both paediatric and adult cohorts) was assessed as part of the procedure EMEA/H/C/005244/P46/005.

The data from Study 11 were not pooled with KOMET due to differences in study design (double blind vs open label single arm), primary endpoints (efficacy vs. PK), and pain measurement tools. KOMET used the NF1-PN-specific PAINS-pNF tool, whereas Study 11 used the NRS-11.

Design and conduct of clinical studies

The Applicant did not conduct a dose response study, the proposed dosage 25 mg/m² BID (capped at 50 mg bid when BSA is ≥ 1.9 m2) is in line with the currently approved dose in paediatric patients which is agreed.

The pivotal study (KOMET) was a double blind randomized placebo controlled study conducted to determine the efficacy, safety and PK of selumetinib in adult participants with symptomatic inoperable NF1-associated PNs.

Participants had to complete a pain diary (PAINS-pNF) with a documented chronic target PN pain score for at least 4 days out of 7 days for at least 2 weeks during the screening period.

The target PN was selected by the investigator as the clinically most relevant PN, which has to be measurable by volumetric MRI analysis (i.e., a PN of at least 3 cm measured in one dimension, which can be seen on at least 3 imaging slices, and has a reasonably well-defined contour).

Participants were randomized 1:1 to receive selumetinib 25 mg/m² BID orally 'with a maximum of 50 mg BID) or placebo for twelve 28-day cycles with no rest periods between cycles. Randomisation was stratified by target PN pain score and geographical regions. Participants in the placebo group crossed over to selumetinib treatment after the end of Cycle 12.

The primary endpoint was defined as the percentage of patients with complete response or confirmed partial response (ORR) by the end of cycle 16. Complete response (CR) was defined as disappearance of the target Plexiform Neurofibroma (PN) and partial response (PR) as PN decrease ≥20% compared to baseline. Responses were considered confirmed if the PR was maintained at the subsequent MRI scan within the 3 to 6 months after first response, as determined by ICR per REiNS criteria.

The MAH decision to have the assessment of the primary endpoint in cycle 16 whereas the crossover of participants from the placebo arm to selumetinib happened in cycle 12 was based on the fact that a confirmed response would require an MRI 3 to 6 months after the start of the response and that participants in the placebo arm who would have had a first response after the crossover were not able to have a confirmatory MRI between cycles 12 and 16.

The Fisher's exact test, employed for the ORR analysis, was not fully aligned with the EMA's guideline on Adjustment for Baseline Covariates in Clinical Trials (EMA/CHMP/295050/2013), which recommends that stratification variables should be incorporated in the primary analysis. An analysis using the Cochran–Mantel–Haenszel test adjusted for the two stratification factors showed results consistent with the primary unadjusted Fisher's exact test analysis, showing no meaningful impact of the adjustment on the ORR by the end of Cycle 16. Given the concordance of the adjusted and unadjusted analyses, and the absence of any indication that the stratification factors influenced the treatment effect, the impact on the robustness of the conclusions is considered negligible.

Key secondary endpoints clinical outcomes including pain and quality of life

As put forward in the Protocol Assistance (PA), the clinical outcome assessments are considered critical to demonstrate the clinical relevance of the observed tumour reduction particularly in the adult population, where PN growth is slower compared to paediatric patients.

PN-related pain improvement was assessed by the difference in change from baseline in Pain Intensity Plexiform Neurofibroma (PAIN-pNF) chronic target PN-pain intensity at Cycle 12 among participants with a PAINSpNF chronic target PN pain intensity score ≥ 3 at baseline. As outlined in the initial and follow-up PA, the PAIN-pNF is not among the REiNS International Collaboration recommended PRO instruments to measure pain intensity. However, the CHMP considered that this tool used to evaluate chronic target PN-pain intensity resembles the classical NRS11 used in pain studies and can be acceptable.

Quality of life improvement was assessed by the difference in change from baseline in PlexiQoL total score at Cycle 12. The PlexiQoL questionnaire is a disease-specific QoL measure for adults with NF1-associated plexiform neurofibromas. Despite not being among the REiNS International Collaboration recommended PRO instruments the PlexiQoL questionnaire received a letter of support as part of a qualification procedure and was deemed of interest in the context of this procedure.

Recruitment: A total of 145 participants (71 selumetinib; 74 placebo) were randomised and included in the FAS, among them 22 (15.2%) discontinued before the end of the Randomized Period. A total of 103 participants were in the Pain FAS; 42 participants (selumetinib: 21; placebo: 21) were excluded since they did not have a baseline PAINS-pNF chronic target PN pain intensity score ≥ 3.

Baseline characteristics: In the FAS, male represented 51.7% of the population, white subjects (55.9%) were the most presented participants and the median age was 29 years (rage 18-60 years). No patients above 65 years of age were included in the study, this limitation was reflected in section 4.2 of the SmPC. The median time from diagnosis of NF1 to start of study was 20.957 years balanced in both groups. The most common reasons for the inoperability of the PN were similar between treatment groups, in particular close proximity to vital structures (total 52.4%), PN invasiveness (total 45.5%), high vascularity (total 30.5%), embedding of the PN in vital structures (total 30.3%).

The main differences between arms were the median target PN tumour volume (selumetinib: 110.18 mL versus placebo: 221.85 mL), the rate of participants with target PN-related disfigurement (selumetinib: 32.4%; placebo: 23.0%) and the percentage of participants with non-target PN tumours (selumetinib: 25.4%; placebo: 40.5%).

Efficacy data and additional analyses

Primary endpoint: At the end of cycle 16 (4 cycles after the end of the randomised period), the percentage of patients with confirmed complete or partial response (ORR) using on-treatment volumetric MRI assessments determined by ICR (per REiNS criteria), was 19.7% (95% CI = 11.2, 30.9) in the selumetinib arm versus 5.4% (95% CI = 1.5, 13.3) in the placebo showing a statistically significantly difference between arms (p = 0.0112; alpha level = 0.047).

Among the 4 responder participants of the placebo arm, 2 had their first response at the end of cycle 12 with a confirmation at cycle 16.

The analysis of ORR by subgroups showed an apparent difference in response in Asian participants (both by race and geographical location), where the ORR trended towards being higher when compared to the global population. However, in the 8 participants who subsequently crossed over from placebo to selumetinib and achieved a cPR, none were Asian (7 participants were White, one participant was Black). Furthermore, results in the PAINS-pNF chronic target PN pain intensity score at Cycle 12 were similarly in Asian and non-Asian participants. It should also be noted that in the initial MAA, in paediatric population results were mostly driven by Caucasians who represented the vast majority of the population in the study (42/50 participants). In addition, in a phase 2 study with selumetinib conducted in adults (Gross, *et al.* 2025[1]), and performed mainly in Caucasian patients (25 out of 33), the reported response rate was 63.6%. In the absence of external validity, nor biological rationale, as per the principles outlined in the Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013), the difference observed between subgroups was not considered credible, and likely a chance finding.

First key secondary endpoint: PAINS-pNF Chronic Target PN Pain Intensity

Difference of the means in the change from baseline in PAINS-pNF Chronic Target PN Pain Intensity Score was evaluate at cycle 12 at the (end of the randomized period) between selumetinib and placebo using MMRM in the Pain FAS. The mean change from baseline in the PAINS-pNF chronic target PN pain intensity between the treatment groups favoured selumetinib but was not statistically significant (LS mean difference = -0.8; 95% CI = -1.6, 0.1; p = 0.070).

Results from sensitivity analyses were directionally consistent with the main analysis of the key secondary endpoint of PAINS-pNF intensity scores during the Randomized Period, suggesting that the amount of missing data and related reasons did not affect the reliability of the primary analysis results and that MAR was a reasonable assumption.

However, the higher frequency of increased chronic pain medication use in the placebo group compared to the selumetinib group may have confounded the interpretation of treatment effects on chronic pain scores.

The clinically significant difference was particularly crucial in an adult population where tumours are expected to grow more slowly than in children.

Second key secondary endpoint: PlexiQoL total score

The difference of the means in the change in the PlexiQoL total score from baseline to cycle 12 (end of the randomized period) was compared between selumetinib and placebo using MMRM in the FAS. The

[1] Gross, A.M., O'Sullivan Coyne, G., Dombi, E. *et al.* Selumetinib in adults with NF1 and inoperable plexiform neurofibroma: a phase 2 trial. *Nat Med* **31**, 105–115 (2025). https://doi.org/10.1038/s41591-024-03361-4

mean change from baseline in the PlexiQoL total score between the treatment groups was not statistically significant (LS mean difference = -0.1; 95% CI = -1.2, 1.1; nominal p = 0.918).

The results for both sensitivity analyses were consistent with the main analysis of the PlexiQoL scores in the FAS during the Randomized Period (data not shown).

A trend favouring selumetinib over placebo was observed on the PAINS-pNF Chronic Target PN Pain Intensity Score, but did not demonstrate a statistically significant difference. As per the hierarchical testing procedure, the difference on PlexiQoL score was not subject to hypothesis testing, and no trend could be observed.

Target PN related secondary endpoint

Among the responders all participants had a confirmed partial response, no complete response was observed. A total of 5 participants had a progressive disease in the placebo arm versus 1 in the selumetinib arm.

The median percentage changes in target PN volume from baseline to the end of cycle 16 were -14.45% (min, max change: -58.1%, 27.6%) in the selumetinib group and -9.21% (min, max change: -44.0%, 29.5%) in the placebo group. However, considering the difference in median volume between arms at baseline, and that from cycle 12 onwards, all patients were treated with selumetinib it is difficult to draw any conclusion.

As data cutoff date, the median time to response (TTR) was 3.73 months (95% CI: 3.61, 11.07).

PRO related secondary endpoint

At the end of Cycle 12, a marginal difference in chronic target PN pain palliation responders was observed: 39.0% participants in the selumetinib group compared to 32.5% participants in placebo group (OR = 1.5; 95% CI = 0.6, 4.0; nominal p = 0.405).

At the end of Cycle 12, a larger reduction in the use of medication for chronic pain from baseline was observed in the selumetinib group compared to placebo in all cycles of the randomised period (OR = 2.2; 95% CI = 0.9, 5.7; nominal p = 0.098).

At the end of Cycle 12, a difference in change from baseline in PII-pNF pain interference total score was observed favouring selumetinib (LS mean difference= -0.5; 95% CI = -0.9, -0.1; nominal p = 0.023).

At the end of Cycle 12, slightly higher numerical scores were observed compared to baseline in both groups and the LS mean difference in change from baseline in PROMIS Physical Function between groups was -0.1 (95% CI: -0.8, 0.7; nominal p = 0.850).

At the end of cycle 12, both treatment groups showed numerically higher scores through Cycle 12 from baseline, in the Skin Sensations domain from the PedsQL. Between groups the LS mean difference was -2.2 (95% CI = -8.8, 4.3; nominal p-value = 0.500).

At Cycle 12 Day 28, slightly higher numerical scores on EQ-5D-5L were observed compared to baseline in both groups the LS mean difference between groups was 0.03 (95% CI = -0.03, 0.09; nominal p = 0.335) favouring selumetinib

Overall, the secondary endpoints appear to be numerically in favour of the treatment group compared with placebo, however the differences are often slight and their clinical relevance has not always been established.

The Applicant also provided data from the final DCO of KOMET study (when the last participant had the opportunity to reach Cycle 24 Day 28 visit) that occurred on 17 March 2025, approximately 8 months after the Primary Analysis (DCO2, 05 August 2024) which was initially submitted with this variation. At the Final Analysis, the median treatment exposure to selumetinib was approximately 2 years versus approximately 1.5 years previously. Data showed sustain reductions in tumour volume (median best percentage change: -16.91% vs -15.75% at Primary Analysis). The median duration of response remained unreached and of 14 participants with confirmed responses at the Primary Analysis, all remained responder for ≥6-month response, and 64.3% for ≥12 months, compared with 68.2% and 21.4%, respectively, at the primary analysis. Following cross-over to selumetinib from placebo after Cycle 12,some improvements in pain-related endpoints and reductions in pain medication use were observed.

2.6.4. Conclusions on the clinical efficacy

The effect of selumetinib on the volume and growth rate of PN in adults has been established in a double blind placebo controlled study, the ORR (per REiNS criteria), was 19.7% (95% CI = 11.2, 30.9) in the selumetinib arm versus 5.4% (95% CI = 1.5, 13.3) in the placebo showing a statistically significant difference between arms (p = 0.0112; alpha level = 0.047). Although no statistically significant correlation was observed between change in pain and change in target PN volume, a numerical improvement was observed on the PAINS-pNF Chronic Target PN Pain Intensity score.

2.7. Clinical safety

Introduction

The primary data for the safety of selumetinib in adult patients with NF1-PN derives from the KOMET study, an international Phase III study in adult participants with inoperable and symptomatic NF1-PN. All participants in the KOMET study are evaluated for safety (AEs, clinical chemistry, haematology, urinalysis, physical examination, vital signs, ECG, ECHO, ophthalmologic assessment, and ECOG performance status) throughout the study.

As per the protocol, data from the randomized period (first 12 cycles) of the study allow for an evaluation of safety relative to a placebo control. Participants who received placebo during the randomized period of KOMET study were crossed over to receive open-label selumetinib treatment after the end of Cycle 12 or earlier if they had documented disease progression. Data collected during the on-selumetinib period allow for evaluation of safety for a larger number of selumetinib-treated participants and provide longer-term safety data for participants originally randomized to selumetinib.

As NF1-PN is a rare disease, the individual studies have small participant populations, pooled data from multiple studies maximizes the participant populations to provide a more accurate estimation of the frequency of common AEs and enables identification of any rare treatment-related AEs that have not yet been identified. Hence the MAH has also submitted safety results from the adult cohort of the study 11.

Study 11 is a single arm phase 1 open label study to assess the safety, tolerability, pharmacokinetics and clinical efficacy of selumetinib, in Chinese paediatric and adult subjects with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). The study comprised 2 independent cohorts, one for paediatric participants and another for adult, each targeting enrolment of around 16 participants.

Komet and study 11 both included adults with NF1-PN and employed the same dosing regimens and similar methods for collecting and assessing AEs and other safety assessments.

Patient exposure

Demographic and baseline characteristics

In the KOMET Phase III study, overall, 51.7% of participants were male; most participants were White (55.9%) or Asian (31.0%). The median age at enrolment was 29 years; age ranged from 18 to 60 years. By age subgroup, 74 participants were 18 to < 30 years of age, and 71 participants were 30 to < 65 years of age. None of the participants in the KOMET study was 65 years of age or older.

Patient exposure

Overall, 137 participants were included in the On-selumetinib SAF, 71 participants randomised to selumetinib and 66 randomized to placebo who crossed over to selumetinib treatment for the Open-label Period.

At the DCO date used for the safety analysis (05 August 2024), the median total duration of selumetinib treatment in NF1-PN adult patients was about 12 months (range: < 1 – 32 months). Of these patients 50.4% of patients were exposed to selumetinib treatment for < 12 months and remaining 49.6% patients were exposed to selumetinib for > 12 months.

As of the DCO date, 33 (22.8%) participants had discontinued study intervention and 112 (77.2%) participants were continuing to receive selumetinib during the Open-label Period. Of the 33 participants who had discontinued study intervention, 22 participants (13 in the selumetinib group and 9 in the placebo group) discontinued during the Randomized Period (before completion of Cycle 12). The number and reasons for discontinuation from treatment were as expected for a study of this duration and patient population and did not raise any concerns about the conduct of the study.

Patient disposition is presented in Table 13 of section 2.6.2. Main study.

Adverse events

Treatment emergent adverse events (TEAEs)

Table 32: Overview of adverse events during the randomized period (KOMET Randomized period SAF)

	Selumetinib (N = 71)	Placebo (N = 74)
AE category	**n (%)**	**n (%)**
Any AE	71 (100)	68 (91.9)
Any AE possibly related to study intervention [a]	68 (95.8)	42 (56.8)
Any AE of CTCAE Gade 3 or higher	23 (32.4)	13 (17.6)
Any AE of CTCAE Grade 3 or higher, possibly related to study intervention	14 (19.7)	1 (1.4)
Any AE with outcome of death	0	0
Any SAE (including events with outcome of death)	10 (14.1)	9 (12.2)
Any SAE (including events with outcome of death), possibly related to study intervention [a]	4 (5.6)	1 (1.4)
Any SAE leading to discontinuation of study intervention	4 (5.6)	4 (5.4)
Any SAE leading to discontinuation of study intervention, possibly related to study intervention [a]	2 (2.8)	0
Any AE leading to discontinuation of study intervention	9 (12.7)	5 (6.8)
Any AE leading to discontinuation of study intervention, possibly related to study intervention [a]	6 (8.5)	1 (1.4)
Any AE leading to dose modification [b]	27 (38.0)	10 (13.5)
Any AE leading to dose interruption of study intervention	19 (26.8)	8 (10.8)
Any AE leading to dose reduction of study intervention	10 (14.1)	3 (4.1)
Any AEs of special interest	47 (66.2)	16 (21.6)

[a] As assessed by the investigator.

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

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

CTCAE version 5.0

Based on DCO date 05-Aug-2024.

Table 33: Overall summary of exposure-adjusted of AEs by exposure period (KOMET on selumetinib SAF)

AE category	Number (%) of participants [exposure-adjusted rate (per 100 person-years)] [a]					
	0 to 12 Cycles		> 12 to 24 Cycles		0 to DCO	
	Selumetinib (N=71) [PY=58.6]	Placebo/ Selumetinib (N=66) [PY=43.9]	Selumetinib (N=57) [PY=38.4]	Placebo/ Selumetinib (N=20) [PY=6.0]	Selumetinib (N=71) [PY=101.8]	Placebo/ Selumetinib (N=66) [PY=49.9]
Any AE	71 (100) [121.2]	62 (93.9) [141.2]	44 (77.2) [114.6]	6 (30.0) [100]	71 (100) [69.7]	62 (93.9) [124.2]
Any AE possibly related to study intervention	67 (94.4) [114.3]	57 (86.4) [129.8]	22 (38.6) [57.3]	4 (20.0) [66.7]	68 (95.8) [66.8]	57 (86.4) [114.2]
Any AE of CTCAE Grade 3 or higher	23 (32.4) [39.2]	12 (18.2) [27.3]	6 (10.5) [15.6]	1 (5.0) [16.7]	29 (40.8) [28.5]	12 (18.2) [24.0]
Any AE of CTCAE Grade 3 or higher, possibly related to study intervention [b]	14 (19.7) [23.9]	4 (6.1) [9.1]	3 (5.3) [7.8]	0	18 (25.4) [17.7]	4 (6.1) [8.0]
Any AE with outcome of death	0	0	0	0	0	0
Any SAE (including events with outcome of death)	9 (12.7) [15.4]	5 (7.6) [11.4]	5 (8.8) [13.0]	0	13 (18.3) [12.8]	5 (7.6) [10.0]
Any SAE (including events with outcome of death), possibly related to study intervention [b]	3 (4.2) [5.1]	0	1 (1.8) [2.6]	0	4 (5.6) [3.9]	0
Any SAE leading to discontinuation of study intervention	4 (5.6) [6.8]	0	0	0	4 (5.6) [3.9]	0
Any SAE leading to discontinuation of study intervention, possibly related to study intervention [b]	2 (2.8) [3.4]	0	0	0	2 (2.8) [2.0]	0
Any AE leading to discontinuation of study intervention	8 (11.3) [13.7]	1 (1.5) [2.3]	1 (1.8) [2.6]	0	9 (12.7) [8.8]	1 (1.5) [2.0]
Any AE leading to dose modification	26 (36.6) [44.4]	20 (30.3) [45.6]	9 (15.8) [23.4]	1 (5.0) [16.7]	30 (42.3) [29.5]	21 (31.8) [42.1]

AE category	Number (%) of participants [exposure-adjusted rate (per 100 person-years)] [a]					
	0 to 12 Cycles		> 12 to 24 Cycles		0 to DCO	
	Selumetinib (N=71) [PY=58.6]	Placebo/ Selumetinib (N=66) [PY=43.9]	Selumetinib (N=57) [PY=38.4]	Placebo/ Selumetinib (N=20) [PY=6.0]	Selumetinib (N=71) [PY=101.8]	Placebo/ Selumetinib (N=66) [PY=49.9]
Any AE leading to dose interruption of study intervention	18 (25.4) [30.7]	20 (30.3) [45.6]	8 (14.0) [20.8]	1 (5.0) [16.7]	22 (31.0) [21.6]	21 (31.8) [42.1]
Any AE leading to dose reduction of study intervention	10 (14.1) [17.1]	5 (7.6) [11.4]	1 (1.8) [2.6]	0	12 (16.9) [11.8]	5 (7.6) [10.0]
Any AEs of special interest	46 (64.8) [78.5]	28 (42.4) [63.8]	10 (17.5) [26.0]	0	47 (66.2) [46.2]	28 (42.4) [56.1]
Any adverse drug reaction	70 (98.6) [119.5]	58 (87.9) [132.1]	23 (40.4) [59.9]	3 (15.0) [50.0]	70 (98.6) [68.8]	58 (87.9) [116.2]

[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. Exposure-adjusted rates = number of participants/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.

[b] As assessed by the investigator.

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

Note: Study D134BC00001 DCO date: 05-Aug-2024.

Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO. CTCAE version 5.0. MedDRA version 26.1

Common adverse event

Table 34: Most common adverse events occurring in ≥ 10% of participants in either treatment group from 0 to DCO by exposure period (KOMET on-selumetinib SAF)

Preferred Term	Number (%) of participants [exposure-adjusted rate (per 100 person-years)] [a]					
	0 to 12 Cycles		> 12 to 24 Cycles		0 to DCO	
	Selumetinib (N=71) [PY=58.6]	Placebo/ Selumetinib (N=66) [PY=43.9]	Selumetinib (N=57) [PY=38.4]	Placebo/ Selumetinib (N=20) [PY=6.0]	Selumetinib (N=71) [PY=101.8]	Placebo/ Selumetinib (N=66) [PY=49.9]
Dermatitis acneiform	42 (59.2) [71.7]	22 (33.3) [50.1]	0	0	42 (59.2) [41.3]	22 (33.3) [44.1]

Preferred Term	Number (%) of participants [exposure-adjusted rate (per 100 person-years)] [a]					
	0 to 12 Cycles		> 12 to 24 Cycles		0 to DCO	
	Selumetinib (N=71) [PY=58.6]	Placebo/ Selumetinib (N=66) [PY=43.9]	Selumetinib (N=57) [PY=38.4]	Placebo/ Selumetinib (N=20) [PY=6.0]	Selumetinib (N=71) [PY=101.8]	Placebo/ Selumetinib (N=66) [PY=49.9]
Blood creatine phosphokinase increased	32 (45.1) [54.6]	18 (27.3) [41.0]	5 (8.8) [13.0]	0	33 (46.5) [32.4]	18 (27.3) [36.1]
Diarrhoea	30 (42.3) [51.2]	9 (13.6) [20.5]	5 (8.8) [13.0]	0	32 (45.1) [31.4]	9 (13.6) [18.0]
Vomiting	18 (25.4) [30.7]	6 (9.1) [13.7]	3 (5.3) [7.8]	1 (5.0) [16.7]	20 (28.2) [19.6]	7 (10.6) [14.0]
Rash	11 (15.5) [18.8]	14 (21.2) [31.9]	2 (3.5) [5.2]	0	13 (18.3) [12.8]	14 (21.2) [28.1]
Nausea	17 (23.9) [29.0]	5 (7.6) [11.4]	2 (3.5) [5.2]	0	18 (25.4) [17.7]	5 (7.6) [10.0]
Paronychia	9 (12.7) [15.4]	9 (13.6) [20.5]	4 (7.0) [10.4]	0	14 (19.7) [13.8]	9 (13.6) [18.0]
Alopecia	13 (18.3) [22.2]	5 (7.6) [11.4]	2 (3.5) [5.2]	0	15 (21.1) [14.7]	5 (7.6) [10.0]
Dry skin	13 (18.3) [22.2]	5 (7.6) [11.4]	0	0	13 (18.3) [12.8]	5 (7.6) [10.0]
Oedema peripheral	10 (14.1) [17.1]	7 (10.6) [15.9]	2 (3.5) [5.2]	0	11 (15.5) [10.8]	7 (10.6) [14.0]
Fatigue	14 (19.7) [23.9]	1 (1.5) [2.3]	2 (3.5) [5.2]	0	16 (22.5) [15.7]	1 (1.5) [2.0]
AST increased	13 (18.3) [22.2]	4 (6.1) [9.1]	0	0	13 (18.3) [12.8]	4 (6.1) [8.0]
ALT increased	11 (15.5) [18.8]	4 (6.1) [9.1]	0	0	11 (15.5) [10.8]	4 (6.1) [8.0]
Anaemia	6 (8.5) [10.2]	9 (13.6) [20.5]	0	0	6 (8.5) [5.9]	9 (13.6) [18.0]
COVID-19	11 (15.5) [18.8]	2 (3.0) [4.6]	1 (1.8) [2.6]	0	12 (16.9) [11.8]	2 (3.0) [4.0]
Headache	8 (11.3) [13.7]	3 (4.5) [6.8]	1 (1.8) [2.6]	0	9 (12.7) [8.8]	3 (4.5) [6.0]
Back pain	5 (7.0) [8.5]	1 (1.5) [2.3]	3 (5.3) [7.8]	0	8 (11.3) [7.9]	1 (1.5) [2.0]
Constipation	7 (9.9) [11.9]	5 (7.6) [11.4]	1 (1.8) [2.6]	0	8 (11.3) [7.9]	5 (7.6) [10.0]
Upper respiratory tract infection	5 (7.0) [8.5]	1 (1.5) [2.3]	3 (5.3) [7.8]	0	8 (11.3) [7.9]	1 (1.5) [2.0]

Note: Study D134BC00001 DCO date: 05-Aug-2024.

Includes AEs starting/worsening after first selumetinib dose until 30 days after last dose or DCO. CTCAE version 5.0. MedDRA version 26.1.

Adverse events by severity

During the randomized period, in the selumetinib group, 19 (26.8%) participants had one or more AEs with a worst severity of grade 3 and 4 (5.6%) participants had one or more AEs with a worst severity of Grade 4 severity. None of the grade 4 events were SAEs. One participant had Grade 4 lipase increased (action taken with study intervention was drug interruption, assessed by the investigator as not related to study intervention, outcome was resolved) and 3 participants had grade 4 events of blood creatine phosphokinase increased.

Table 35: Adverse events of CTCAE grade 3 or higher in 2 or more participants during the randomized period, by system Organ class, preferred term (Randomized Period SAF)

System Organ Class Preferred Term	Selumetinib (N = 71)	Placebo (N = 74)
	n (%)	n (%)
Participants with AE of CTCAE grade 3 or higher	23 (32.4)	13 (17.6)
Infections and infestations	6 (8.5)	1 (1.4)
Cellulitis	2 (2.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.8)	3 (4.1)
Neurofibrosarcoma	1 (1.4)	3 (4.1)
Nervous system disorders	4 (5.6)	3 (4.1)
Headache	2 (2.8)	1 (1.4)
Gastrointestinal disorders	2 (2.8)	1 (1.4)
Abdominal pain	2 (2.8)	0
Skin and subcutaneous tissue disorders	2 (2.8)	0
Dermatitis acneiform	2 (2.8)	0
Musculoskeletal and connective tissue disorders	1 (1.4)	2 (2.7)
Muscular weakness	0	2 (2.7)
Investigations	10 (14.1)	1 (1.4)
Blood creatine phosphokinase increased	5 (7.0)	1 (1.4)
GGT increased	2 (2.8)	0

Note: Number (%) of participants with AEs of CTCAE grade 3 or higher, sorted by international order for SOC and alphabetically for PT. Participants with multiple AEs of CTCAE grade 3 or higher were counted once for each SOC/PT. CTCAE version 5.0. MedDRA version 26.1.

Note: Based on DCO date 05 August 2024

Adverse reaction

The ADRs were assessed based on factors such as the frequency of reporting relative placebo, the timing of the event relative to the time of drug exposure, the extent to which the event was consistent with the pharmacology of selumetinib, the known safety profile of selumetinib in the paediatric

population with inoperable NF1-PN, and whether the event was observed in NF1-PN patients as part of their disease/disease burden.

Table 36: ADRs identified in adult patients in the selumetinib NF1-PN studies and compared to paediatric patients:

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 74)		KOMET Study [b] (N = 137)	
	Overall Frequency (All CTCAE Grades) [c]	Frequency of CTCAE Grade 3 and above [d]	Overall Frequency (All CTCAE Grades) [c]	Frequency of CTCAE Grade 3 and above [e]
Eye disorders				
Vision blurred ^	Very Common (15%)	-	Common (4%)	-
Retinal pigment epithelial detachment (RPED)/ Central serous retinopathy (CSR) * ††	-	-	Uncommon (0.6%)	-
Retinal vein occlusion (RVO) * ††	-	-	Uncommon (0.3%)	-
Respiratory, thoracic and mediastinal disorders				
Dyspnoea *	Common (8%)	-	Common (3%)	Common (1%)
Gastrointestinal disorders				
Vomiting ^	Very common (86%)	Common (9%)	Very common (20%)	-
Diarrhoea ^	Very common (81%)	Very common (15%)	Very common (30%)	-
Nausea ^	Very common (77%)	Common (3%)	Very common (17%)	-
Stomatitis ^*	Very common (55%) $	Common (1%) $	Very common (14%) £	Common (1%) £
Constipation	-	-	Very common (10%)	-
Dry mouth	Common (5%)	-	Common (6%)	-
Skin and subcutaneous tissue disorders				
Dry skin	Very common (65%)	Common (1%)	Very common (13%)	-
Dermatitis acneiform	Very common (61%)	Common (4%)	-	-
Rashes (acneiform) ^*	-	-	Very common (55%)	Common (2%)

MedDRA SOC and MedDRA term	Paediatric Pool [a] (N = 74)		KOMET Study [b] (N = 137)	
	Overall Frequency (All CTCAE Grades) [c]	**Frequency of CTCAE Grade 3 and above [d]**	**Overall Frequency (All CTCAE Grades) [c]**	**Frequency of CTCAE Grade 3 and above [e]**
Paronychia^	Very common (57%)	Very common (14%)	Very common (17%)	Common (3%)
Rashes (non-acneiform) ^*	Very common (53%)	Common (3%)	Very common (27%)	Common (1%)
Hair changes ^*	Very common (39%)	-	Very common (18%)	-
General disorders				
Pyrexia	Very common (61%)	Common (8%)	Common (5%)	Common (1%)
Asthenic events *	Very common (59%)	-	Very common (15%)	-
Peripheral oedema *	Very common (31%)	-	Very common (16%)	-
Facial oedema *	Common (8%) $	-	Common (4%) £	-
Investigations [f]				
Blood CPK increased ^	Very common (77%)	Common (9%)	Very common (37%)	Common (7%)
Haemoglobin decreased *	Very common (54%)	Common (3%)	Very common (11%)	Common (2%)
AST increased	Very common (51%)	Common (1%)	Very common (12%)	Common (1%)
Blood albumin decreased *	Very common (51%)	-	Common (2%)	-
ALT increased	Very common (39%)	Common (3%)	Very common (11%)	Common (1%)
Blood creatinine increased	Very common (32%)	Common (1%)	Common (2%)	-
Ejection fraction decreased ^	Very common (28%)	Common (1%)	Common (7%)	Common (1%)
Increased blood pressure *	Very common (18%)	-	Common (4%)	Common (2%)

[a] NF1-PN Paediatric Pool data (N = 74) is pooled from SPRINT Phase I (N = 24), SPRINT Phase II, Stratum 1 (N = 50). Frequency percentage numbers are rounded to the nearest full number.

[b] NF1-PN adult patients data is from KOMET study (N = 137). Frequency percentage numbers are rounded to the nearest full number.

[c] Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), all studies used CTCAE v5.0, except for SPRINT paediatric study which used CTCAE v4.03.

[d] All events were CTCAE grade 3, except for one CTCAE grade 4 event of blood CPK increased and one CTCAE grade 4 event of blood creatinine increased. There were no deaths.

[e] All events were CTCAE grade 3, except for one CTCAE grade 4 event of pyrexia and four CTCAE grade 4 events of blood CPK increased. There were no deaths.

[f] In the SPRINT study, all lab abnormalities were reported as AEs. In other studies included in the NF1-PN paediatric and adult patients, lab abnormalities were only reported as AEs when they met SAE criteria, resulted in discontinuation, or were clinically relevant as judged by the investigator.

CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase
^ See Description of selected adverse reactions

[††] Identified ADRs from other clinical trial experience in adult patients (N = 347), with multiple tumour types, receiving treatment with selumetinib (75 mg twice daily). These ADRs have not been reported in paediatric or adult population with NF1 who have inoperable PN.

[*] ADRs based on grouping of individual Preferred Terms (PT):
Asthenic events: fatigue, asthenia
Blood albumin decreased: hypoalbuminaemia, blood albumin decreased
CSR/RPED: detachment of macular retinal pigment epithelium, chorioretinopathy
Dyspnoea: dyspnoea exertional, dyspnoea, dyspnoea at rest
Facial oedema: periorbital oedema, face oedema ([$] grouping for paediatric pool only)
Facial oedema: periorbital oedema, face oedema, lip swelling, eyelid oedema, swelling face ([£] grouping for KOMET study only)
Haemoglobin decreased: anaemia, haemoglobin decreased
Hair changes: alopecia, hair colour change
Increased blood pressure: blood pressure increased, hypertension
Peripheral oedema: oedema peripheral, oedema, localised oedema, peripheral swelling
Rashes (acneiform): dermatitis acneiform, acne, folliculitis
Rashes (non-acneiform): rash pruritic, rash maculo-papular, rash papular, rash, rash erythematous, rash macular
RVO: retinal vascular disorder, retinal vein occlusion, retinal vein thrombosis
Stomatitis: stomatitis, mouth ulceration ([$] grouping for paediatric pool only)
Stomatitis: stomatitis, mouth ulceration, aphthous ulcer, gingival swelling ([£] grouping for KOMET study only)

In the NF1-PN adult patients, LVEF reduction (PT: ejection fraction decreased) was reported in 10 (7%) patients; in 2 (1.5%) patients, LVEF decrease led to dose interruption. At the time of analysis, 7 of the 10 patients had recovered. The median time to first occurrence of LVEF reduction was 342 days (approximately 11 months) [median duration 112.5 days (approximately 4 months)].

For the ocular toxicity, CTCAE grade 1 event of blurred vision was reported in 5 (4%) patients. One patient (0.7%) required dose interruption. All events were managed without dose reduction and at the time of analysis, all 5 patients had recovered.

For the blood CPK increase, the median time to first onset of the maximum CTCAE grade blood CPK increase was 167 days (approximately 6 months), and the median duration of maximum grade event was 122 days (approximately 4 months). Forty-two patients (30.7%) had maximum CTCAE grade of 1 or 2. A maximum CTCAE grade 3 events occurred in 5 (3.6%) patients, and CTCAE grade 4 events occurred in 4 (2.9%) patients. Six patients had an event of blood CPK increase that led to dose interruptions and dose reduction was required in 3 patients. At the time of analysis, 21 of the 51 patients had recovered.

Serious adverse event/deaths/other significant events

Serious adverse events

A similar proportion of participants in the selumetinib (10 [14.1%] participants) and placebo (9 [12.2%] participants) groups had at least 1 SAE during the Randomized Period of the KOMET study. Events reported in more than 1 participant in either treatment group were cellulitis (2 participants in the selumetinib group) and neurofibrosarcoma (3 participants in the placebo group). All other SAEs were reported for 1 participant each.

Events of cellulitis in 2 participants and events of headache and psychiatric decompensation in 1 participant each in the selumetinib group and bacterial urinary tract infection in 1 participant in the placebo group were assessed by the Investigator as possibly related to treatment. One event of cellulitis and the event of psychiatric decompensation led to the discontinuation of study treatment.

Table 37: **Number of subjects with serious adverse events, by system organ class and preferred term (Randomised period safety analysis set)**

System organ class Preferred term	Number (%) of subjects [a] Selumetinib 25 mg/m2 BID (N=71)	 Placebo (N=74)
Subjects with any SAE	10 (14.1)	9 (12.2)
Infections and infestations	3 (4.2)	1 (1.4)
Cellulitis	2 (2.8)	0
Pneumonia	1 (1.4)	0
Urinary tract infection bacterial	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.8)	3 (4.1)
Neurofibrosarcoma	1 (1.4)	3 (4.1)
Neurofibrosarcoma recurrent	1 (1.4)	0
Metabolism and nutrition disorders	0	1 (1.4)
Decreased appetite	0	1 (1.4)
Psychiatric disorders	1 (1.4)	0
Psychiatric decompensation	1 (1.4)	0
Nervous system disorders	2 (2.8)	1 (1.4)
Headache	1 (1.4)	0
Paraparesis	1 (1.4)	0
Seizure	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	1 (1.4)
Acute respiratory failure	0	1 (1.4)
Dyspnoea	1 (1.4)	0
Gastrointestinal disorders	0	1 (1.4)
Dental caries	0	1 (1.4)
Renal and urinary disorders	0	1 (1.4)
Nephrolithiasis	0	1 (1.4)
Injury, poisoning and procedural complications	1 (1.4)	1 (1.4)
Accident	0	1 (1.4)
Joint dislocation	1 (1.4)	0

[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple SAEs are counted once for each system organ class/preferred term.
Includes only SAEs that are treatment emergent during the randomised period. Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 26.1. SAE Serious adverse event.
Randomised period safety analysis set - subjects who received any amount of study intervention in the randomised period.
Randomised safety period - first dose date until earliest of; last dose of Cycle 12, crossover, 30 days after discontinuation, day prior to start of subsequent therapy, or data cut-off.

During the On-selumetinib period, 13 (18.3%) participants in the selumetinib group and 5 (8.8%) participants in the placebo/selumetinib group had SAEs. All events in the placebo/selumetinib group occurred during the first 12 cycles after the crossover to selumetinib treatment and included kidney infection, sepsis, tumour haemorrhage, blurred vision, hematoma, drug withdrawal syndrome, puncture site haemorrhage, and pyrexia. Events in the selumetinib group that occurred during the open-label period (> 12 cycles of selumetinib treatment) included COVID-19 infection, skin infection, clear cell renal carcinoma, back pain, and scrotal swelling. None of these events were assessed by the Investigator as related to study treatment.

Table 38: Number of subjects with serious adverse events, by system organ class and preferred term (On-selumetinib safety analysis set)

	Number (%) of subjects [a] [exposure-adjusted rate (per 100 person-years)]		
System organ class Preferred term	Selumetinib 25 mg/m2 BID (N=71)	Placebo / Selumetinib 25 mg/m2 BID (N=66)	Total (N=137)
Subjects with any SAE	13 (18.3) [13.7]	5 (7.6) [10.3]	18 (13.1) [12.5]
Infections and infestations	4 (5.6) [4.0]	1 (1.5) [2.0]	5 (3.6) [3.3]
COVID-19	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Cellulitis	2 (2.8) [1.9]	0	2 (1.5) [1.3]
Kidney infection	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Pneumonia	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Sepsis	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Skin infection	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (4.2) [2.9]	1 (1.5) [2.0]	4 (2.9) [2.6]
Clear cell renal cell carcinoma	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Neurofibrosarcoma	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Neurofibrosarcoma recurrent	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Tumour haemorrhage	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Psychiatric disorders	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Psychiatric decompensation	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Nervous system disorders	2 (2.8) [2.0]	0	2 (1.5) [1.3]
Headache	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Paraparesis	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Eye disorders	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Vision blurred	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Vascular disorders	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Haematoma	0	1 (1.5) [2.0]	1 (0.7) [0.7]
Respiratory, thoracic and mediastinal disorders	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Dyspnoea	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Musculoskeletal and connective tissue disorders	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Back pain	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Reproductive system and breast disorders	1 (1.4) [1.0]	0	1 (0.7) [0.7]
Scrotal swelling	1 (1.4) [1.0]	0	1 (0.7) [0.7]

[a] Number (%) of subjects with SAEs, sorted by international order for system organ class and alphabetically for preferred term. Subjects with multiple SAEs are counted once for each system organ class/preferred term.
Includes only SAEs that are treatment emergent during the on-selumetinib period. Percentages are based on the total numbers of subjects in the treatment group (N). MedDRA version 26.1. SAE Serious adverse event.
On-selumetinib safety analysis set - subjects who received any amount of selumetinib in the on-selumetinib period.
On-selumetinib safety period - first dose of selumetinib until earliest of; 30 days after discontinuation, day prior to start of subsequent therapy or data cut-off.
Exposure-adjusted rates=100*n subject with SAE/ total on-selumetinib person-years (=sum of all individual exposure durations until SAE start in the on-selumetinib period). Subjects with no SAE are censored to last dose + 30 days or data-cut off date.

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- ***Deaths***

Two adult participants in the KOMET study died more than 30 days after their withdrawal from the study. Both participants were randomized to the placebo group and did not receive any dose of selumetinib on the study.

Of note, four deaths have been reported in the selumetinib NF1-PN clinical program. None occurred while participants were on study.

- ***Adverse events of special interest***

Prespecified AESIs for the adult participants include events in the categories of ocular toxicity, hepatotoxicity, muscular toxicity, and cardiac toxicity.

During the randomized period of the KOMET study, AESIs were reported in a greater proportion of participants in the selumetinib group (47 [66.2%]) than in the placebo group (16 [21.6%] participants). The most common AESIs reported in the selumetinib group were in the category of muscular toxicity (blood creatine phosphokinase increased), hepatotoxicity (increased AST and ALT), and cardiac toxicity (oedema peripheral). The AESIs were generally Grade 1 or Grade 2. Two participants in the selumetinib group had Grade 3 blood creatine phosphokinase increased, and 3 participants had Grade 4 blood creatine phosphokinase increased. The other Grade 3 AESIs were ejection fraction decreased, ALT increased, and AST increased 1 participant each in the selumetinib group), muscular weakness (2 participants in the placebo group), and blood creatine phosphokinase increased (1 participant in the placebo group). None of the AESIs led to the discontinuation of study treatment.

In the selumetinib group during the Randomized Period, the dose was reduced for AESIs of blood creatine phosphokinase increased (2 participants), ALT increased (2 participants), AST increased (2 participants), and oedema peripheral (1 participant).

Most cases of blood creatine phosphokinase increased were asymptomatic and were not associated with other AESIs in the muscular toxicity category. Three participants (2 in the selumetinib group and 1 in the placebo group) had more than 1 muscular toxicity AESI at the same time.

- 1 participant in the selumetinib group had blood creatine phosphokinase increased at baseline which worsened to Grade 3 in severity on Day 28. The event ended on Day 238. Study intervention was interrupted. During this interval, the participant also experienced myalgia (Grade 1, study intervention interruption), 4 intermittent events of myoglobin blood increased (all Grade 1, none required dose modification). On Day 252, the participant had an AE of blood creatine phosphokinase increased (Grade 2, no dose modification). All events resolved and were assessed by the investigator as possibly related to study intervention.

- 1 participant in the selumetinib group had blood creatine phosphokinase increased on Day 26 to Day 78 (worst severity of Grade 4, dose reduced, resolved), myoglobin blood increased on Day 68 (Grade

1, no dose modification, ongoing as of DCO date), and blood creatine phosphokinase increased on Day 85 (worst severity of Grade 3, dose interruption, ongoing as of DCO date); all events were assessed by the investigator as possibly related to study intervention.

▪ 1 participant in the placebo group had myalgia on Day 1 (Grade 1, no dose modification, resolved on Day 6, and assessed by the investigator as possibly related to study intervention) and muscular weakness on Day 71 (Grade 3; study intervention interrupted, resolved on same day, and assessed by the investigator as not related to study intervention).

None of the muscular toxicity AESIs were SAEs or led to discontinuation of study intervention. No events of myopathy or rhabdomyolysis were reported.

In the cardiac toxicity category, none of the participants had overlapping AESIs of decreased ejection fraction with events of oedema/swelling. All events had resolved by the DCO. No events of cardiomyopathy or heart failure were reported.

KOMET On-Selumetinib Period: Across both treatment groups of the KOMET study, 75 (54.7%) of 137 participants who received selumetinib during the on-selumetinib period had at least 1 AESI. Most of the events in the selumetinib group occurred during the Randomized Period. In the placebo/selumetinib group, 28 (42.4%) of 66 participants had at least 1 AESI following crossover to selumetinib. These events were consistent with the events reported for the selumetinib group during the randomized period and included muscular toxicity (18 [27.3%] participants), primarily blood creatine phosphokinase increased; and cardiac toxicity (12 [18.2%] participants), primarily peripheral oedema.

As was the case during the randomized period, maximum severity for most events reported during the open-label period of KOMET was Grade 1 or Grade 2. Two participants in the placebo/selumetinib group had Grade 3 events of blood creatine phosphokinase increased; 1 participant had a Grade 4 event of blood creatine phosphokinase increased. None of the events in the placebo/selumetinib group led to dose reduction or treatment discontinuation.

Laboratory findings

Haematology

Mean values for haematology parameters in both treatment groups were generally stable throughout the Randomized Period of the KOMET study. The mean changes in haematology parameters at the end of the Randomized Period were generally greater in the selumetinib group than in the placebo group, but the changes overall were slight and mean values remained similar in both treatment groups. Most participants had normal (Grade 0) haematology values at baseline that remained within normal limits at the end of the Randomized Period.

No clinically meaningful trends were identified throughout the on-selumetinib period.

Clinical chemistry

Mean values for most clinical chemistry parameters were generally unchanged in both treatment groups throughout the Randomized Period of the KOMET study. The changes overall were slight and mean values remained within normal limits. Most participants had normal clinical chemistry values at baseline that remained within normal limits at the end of the Randomized Period. Shifts to Grade 3 or 4 values were infrequent but occurred more often in the selumetinib group.

No clinically meaningful trends were identified throughout the on-selumetinib period of the KOMET study.

Vital signs, physical finding and other observations related to safety

No clinically meaningful changes from baseline were noted in vital signs at each post-baseline visit in either treatment group during the Randomized Period of the KOMET study.

Safety in special populations

Intrinsic Factors

▪ Sex

The KOMET Randomized Period SAF included 75 (51.7%) males and 70 (48.3%) females. A review of the overall AE profile during the randomized period did not identify any clinically meaningful differences in the overall AE profile between males and females. A greater proportion of females in the selumetinib group had dose interruptions for AEs; however, as this difference was also observed in the placebo group, it likely reflects differences in patient management between males and females.

▪ Age

Participants in the KOMET study were allocated to 1 of 3 prespecified age groups for subgroup analysis (18 to < 30 years, 30 to < 65 years, and ≥ 65 years). The 18 to < 30 years group included 74 participants, and the 30 to < 65 years group included 71 participants. None of the participants were ≥ 65 years of age. A review of the overall AE profile for the 2 age groups did not identify any obvious differences based on age. A greater proportion of older participants had AEs leading to discontinuation of study treatment, but this pattern was also seen in the placebo group, which suggests it does not reflect a real treatment difference.

▪ Race

Most of the participants in the KOMET study were White (N = 81) or Asian (N = 45). Ten participants were of Other race and 9 were Black or African American. A comparison of the AE profiles for the White and Asian racial groups did not identify any clinically meaningful differences or treatment-related trends. The small number of Black or African American participants and participants of other race precluded meaningful interpretation.

▪ Ethnicity

The great majority of participants in the KOMET study and the adult capsule pool were non-Hispanic or Latino. Among the 148 participants in the adult capsule pool for whom ethnicity was reported, 135 (91.2%) were not Hispanic or Latino and 13 (8.8%) participants were Hispanic or Latino. Small numbers in the Hispanic or Latino preclude any meaningful interpretation, but no trends were observed in the overall AE profile between the 2 ethnic groups.

▪ Effect of Geographical Region

Of the 145 participants in the KOMET study, 54 (37.2%) were from Europe, 39 (26.9%) were from Asia, 37 (25.5%) were from the rest of world region, and 15 (10.3%) were from North America (US and Canada). No apparent differences were noted in the overall AE profiles or type and frequency of events across the geographic regions

Extrinsic factors

▪ Effect of food

The effect of food on selumetinib exposure has been evaluated in the selumetinib clinical development program.

▪ Use in Pregnancy and Lactation

Women of Childbearing Potential/Contraception in Males and Females

Selumetinib can cause foetal harm when administered to a pregnant woman. Women of childbearing potential and males with female partners of reproductive potential should use effective contraception methods during treatment with selumetinib and until 1 week after the last dose.

Pregnancy

In animal reproduction studies, administration of selumetinib to mice during organogenesis caused reduced foetal weight, adverse structural defects, and effects on embryofoetal survival at approximate exposures > 5 times the human exposure at the clinical dose of 25 mg/m2 bid.

No pregnancies were reported in any selumetinib clinical study up to the DCO for this submission.

Breastfeeding

Selumetinib and its active metabolite were present in milk from mice dosed with selumetinib throughout gestation and lactation, with a mean plasma/milk ratio of 1.5 in lactating dams dosed at 5 mg/kg bid. Administration of selumetinib to dams during gestation and early lactation was associated with AEs in pups, including reduced growth rates and incidence of malformations.

There are no data on the presence of selumetinib or its active metabolite in human milk or their effects on the breastfed child or milk production. A risk to the newborns/infants cannot be excluded. Due to the potential for adverse reactions in a breastfed child, selumetinib should not be used during breastfeeding and breastfeeding should not be initiated until 1 week after the last dose.

Fertility

The effect of selumetinib on human fertility has not been evaluated. Animal studies do not indicate any potential effect on fertility at therapeutically relevant doses.

▪ Overdose, drug abuse, withdrawal and rebound

The clinical study program and postmarketing experience have not identified the potential for overdose as a safety issue. While there have been some reports of overdose with selumetinib, most cases were accidental in nature or the result of incorrectly recorded BSA and involved only slight increases above the prescribed dose. A review of the safety information for participants who received more than the prescribed dose of selumetinib in a clinical trial did not reveal any unexpected events suggestive of overdose.

Of the studies described in this safety summary, only 1 participant had an AE (diarrhoea) that was attributed to overdose. This event was Grade 1, non-serious, and did not require dose reduction or discontinuation of study treatment. None of the participants in the NF1-PN Adult Capsule Pool or NF1-PN Paediatric Capsule Pool described in this safety summary had an AE that was reported as a PT of overdose.

Inadvertent misdosing of selumetinib, such as administration of a higher selumetinib dose than stated in the protocol or any dose received above the dosage as outlined in the label, should be followed up and treated with appropriate supportive care until recovery. There is no specific treatment for overdose. Due to low elimination of selumetinib related material in urine, dialysis is unlikely to influence the elimination during overdose. Physicians should follow general supportive measures and should treat the patient symptomatically.

The potential for drug abuse has not been investigated in clinical studies of selumetinib. Based on its mode of action, physiological and pharmacological activity, and lack of stimulant properties, selumetinib does not have a potential for drug abuse, and no findings during the clinical study program indicate that selumetinib induces drug abuse.

No formal studies for withdrawal or rebound effects associated with selumetinib treatment have been conducted. Based on its pharmacological properties, selumetinib is not likely to have any withdrawal or rebound effect.

▪ Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies to establish the effects of selumetinib on the ability to drive and use machinery have been conducted. Selumetinib may have a minor influence on the ability to drive and use machines. Fatigue, asthenia, and visual disturbances have been reported during treatment with selumetinib and patients who experience these symptoms should observe caution when driving or using machinery.

Safety related to drug-drug interactions and other interactions

Drug interaction analyses with selumetinib were conducted in the selumetinib clinical development program.

Strong or moderate inducers of CYP3A4 were prohibited during the KOMET study. Concomitant use of strong or moderate inhibitors of CYP3A4 or CYP2C19, with the exception of chronic PN medication, was also to be avoided. In cases where concomitant use of selumetinib with strong or moderate CYP3A4 or CYP2C19 inhibitors was unavoidable, the selumetinib dose was to be reduced. Substrates of OAT3, supplemental vitamin E, and anticoagulant medications (e.g. warfarin) were also to be administered with caution.

A review of the data from the KOMET study did not reveal any significant AEs related to potential toxicity from concurrent administration of selumetinib and prohibited medications. Most of the events that occurred in participants who received a prohibited medication were known ADRs with selumetinib. No new or more severe AEs were reported when concomitant prohibited medication was administered. None of the participants had any SAEs related to a potential toxicity due to drug-drug interaction during the concomitant administration of these medications and selumetinib.

A separate analysis of the NF1-PN Adult Capsule Pool was conducted to assess the potential effects of commonly used medications on selumetinib safety. In this analysis, AEs were summarized by SOC and PT for subsets of participants who received common concomitant medications (defined as a medication by ATC3 classification that was received by 20% of participants).

The data show that the type and frequency of AEs experienced by participants who received these commonly used medications were not different from the profile for the entire NF1-PN Adult Capsule Pool. No specific trend was observed, and no new safety concerns were identified with concomitant administration of selumetinib with any of the medications commonly prescribed for patients with NF1-PN.

Discontinuation due to adverse events

Adverse events leading to discontinuation of treatment

During the KOMET randomized period, 9 (12.7%) participants in the selumetinib group and 5 (6.8%) participants in the placebo group had at least 1 AE that led to treatment discontinuation. The events in the selumetinib group were dermatitis acneiform (2 participants), and cellulitis, neurofibrosarcoma,

neurofibrosarcoma recurrent, psychiatric decompensation, ulcerative keratitis, nausea, nail disorder, and wound (1 participant each). The events of dermatitis acneiform (2 participants), cellulitis, psychiatric decompensation, ulcerative keratitis, nausea, and nail disorder (1 participant each) were assessed as possibly related to study treatment.

The AEs leading to treatment discontinuation in the placebo group included neurofibrosarcoma (3 [4.1%] participants), and decreased appetite and stomatitis (1 [1.4%] participant each).

Table 39: Adverse Events Occurring During the Randomized Period Which Led to Discontinuation of Study Intervention, by System Organ Class and Preferred Term (Randomized Period SAF)

System Organ Class Preferred Term	Selumetinib (N = 71)	Placebo (N = 74)
	n (%)	n (%)
Participants with any AE leading to discontinuation of study intervention	9 (12.7)	5 (6.8)
Infections and infestations	1 (1.4)	0
Cellulitis	1 (1.4)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.8)	3 (4.1)
Neurofibrosarcoma	1 (1.4)	3 (4.1)
Neurofibrosarcoma recurrent	1 (1.4)	0
Metabolism and nutrition disorders	0	1 (1.4)
Decreased appetite	0	1 (1.4)
Psychiatric disorders	1 (1.4)	0
Psychiatric decompensation	1 (1.4)	0
Eye disorders	1 (1.4)	0
Ulcerative keratitis	1 (1.4)	0
Gastrointestinal disorders	1 (1.4)	1 (1.4)
Nausea	1 (1.4)	0
Stomatitis	0	1 (1.4)
Skin and subcutaneous tissue disorders	3 (4.2)	0
Dermatitis acneiform	2 (2.8)	0
Nail disorder	1 (1.4)	0
Injury, poisoning and procedural complications	1 (1.4)	0
Wound	1 (1.4)	0

Note: Number (%) of participants with AEs leading to discontinuation of study intervention, sorted by international order for SOC and alphabetically for PT. Participants with multiple AEs leading to discontinuation of study intervention were counted once for each SOC/PT.

Based on DCO date 05 August 2024

Source: Table 14.3.5.1.1

During the Open-label Period, 1 participant who switched from placebo to selumetinib at the end of the Randomized Period had an AE of postoperative wound complication that led to treatment discontinuation. The event was assessed as Grade 1 and unrelated to study treatment. One participant in the selumetinib group had an SAE of small intestine neuroendocrine tumour during the safety follow-up period. All other AEs leading to treatment discontinuation across the On-selumetinib Period occurred during the Randomized Period.

Adverse events leading to dose modification

During the Randomized Period of the KOMET study, more participants in the selumetinib group (27 [38.0%] participants) had AEs leading to dose modification than in the placebo group (10 [13.5%] participants). AEs leading to dose interruption were reported for 19 (26.8%) participants in the selumetinib group and 8 (10.8%) participants in the placebo group. In the selumetinib group, AEs leading to dose interruption in more than one participant included blood creatine phosphokinase increased (3 [4.2%] participants), and COVID-19, headache, abdominal pain, and nausea (2 [2.8%] participants each).

AEs led to dose reduction for 10 (14.1%) participants in the selumetinib group and 3 (4.1%) participants in the placebo group. In the selumetinib group, the AEs leading to dose reduction for 2 or more participants included paronychia, alopecia, ALT increased, AST increased, and blood creatine phosphokinase increased; all other AEs leading to dose reduction occurred in 1 participant each. In the placebo group, all AEs leading to dose reductions occurred in 1 participant each.

The dose interruptions and reductions did not have a significant effect on relative dose intensity, with most participants receiving 100% of the planned dose.

Post marketing experience

To date, KOSELUGO has received 31 marketing authorization approvals worldwide (60 countries) for the treatment of paediatric patients with NF1 who have symptomatic, inoperable PN.

The safety profile of selumetinib was summarized in the most recent Periodic Benefit Risk Evaluation Report covering the period 10 October 2023 through to 09 April 2024.

As of 09 April 2024, the cumulative world-wide post-approval patient exposure since launch was estimated to be between 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).

Overall, there have been no newly identified safety concerns or significant new safety information received since the granting of the original authorisation for KOSELUGO in paediatric patients with NF1 who have symptomatic inoperable PN.

2.7.1. Discussion on clinical safety

The pivotal KOMET study is the basis for the assessment of the safety profile of selumetinib in adult patients.

Safety data from study 11 are only considered as supportive.

<u>Demographic and baseline characteristics</u>

In the KOMET Phase III study, the demographic and baseline disease characteristics were generally similar between the selumetinib and placebo groups and representative of patients with NF1 who have symptomatic, inoperable PN. Minor imbalances in some demographics and baseline disease

characteristics between the selumetinib and placebo groups were not considered to affect the interpretation of safety results.

Adverse events

The median actual treatment duration during the Randomized Period was 334.0 days (range: 10 to 361) in the selumetinib group and 332.0 days (range: 54 to 350) in the placebo group.

- *Treatment-emergent adverse events (TEAEs)*

The most common SOCs in the selumetinib group belonged to the SOC "Skin and subcutaneous tissue disorders" (selumetinib 90.1% and placebo 35.1%) and "Gastrointestinal disorders" (selumetinib: 74.6%; placebo: 43.2%).

The following PTs occurred in a higher percentage (≥ 5%) of participants in the selumetinib group compared to the placebo group: dermatitis acneiform, alopecia, dry skin, rash, acne, diarrhoea, vomiting, nausea, stomatitis, and constipation, blood creatine phosphokinase increased, AST increased, and ALT increased, fatigue, oedema peripheral, paronychia, back pain, and insomnia.

The rate of fatigue and gastrointestinal events (diarrhoea, nausea, and vomiting) was higher in the selumetinib group, while the rates of rash and anaemia were greater in the placebo/selumetinib group.

- *Adverse events by relationship*

The most frequently reported treatment-related events during the On-selumetinib Period were consistent with the events assessed as treatment-related during the Randomized Period and included dermatitis acneiform, blood creatine phosphokinase increased, and paronychia.

Overall, the AEs reported in the KOMET study related to selumetinib were consistent with the ADRs listed in the product information of selumetinib in paediatric patients.

However, the following new ADRs have been identified for selumetinib: constipation (frequency very common, 10%), rashes acneiform (very common 55%, and a frequency of grade 3 and above of 2%), mouth ulceration, aphthous ulcer, and gingival swelling (added to the existing medical concept of stomatitis), lip swelling, eyelid oedema, and swelling face (added to the existing medical concept of facial oedema).

These new adverse drug reactions have been added to section 4.8 of the SmPC.

Back pain and insomnia were newly observed as occurring in > 5% more selumetinib participants than placebo participants. However, after review of the cases, these were not considered causally related to selumetinib.

Adverse event of special interest

Adverse events of special interest to adult patients treated with selumetinib include the categories of ocular toxicity, hepatotoxicity, muscular toxicity, and cardiac toxicity. Overall, AESI reported in KOMET study are consistent with those observed in paediatric patient. Hence, the most common AESIs reported in the selumetinib group were in the category of muscular toxicity (blood creatine phosphokinase increased), hepatotoxicity (increased AST and ALT), and cardiac toxicity (oedema peripheral and ejection fraction decreased). Description of these AESI for adults have been added to the section 4.8 of the SmPC.

Two patients under selumetinib experienced noteworthy AEs linked to muscular toxicity: one patient under selumetinib treatment had blood CPK increased at baseline that worsening to grade 3 during selumetinib and needed study interruption. This patient also developed myalgia and 4 events of

myoglobin blood increased. Another patient had 2 events of blood CPK increased, grade 4 and grade 3 leading to dose interruption, and experienced myoglobin blood increased. The adverse events of myalgia and myoglobin blood increased experienced by these two patients were further discussed and it was agreed that currently the underlying disease and associated comorbidities may have contributed to the development of these events and that no clear causal association with selumetinib can be established. These adverse events will be monitored through routine pharmacovigilance routine.

Serious AEs and death

- *Serious AEs*

No new safety concerns were identified from SAEs reported in KOMET study.

- *Death:*

No death occurred under selumetinib treatment

Discontinuation and dose modifications due to adverse events

No new AEs related to selumetinib leading to the drug discontinuation or to dose modification were identified.

Other safety findings

From laboratory (haematology, clinical chemistry) and other findings (notably vital signs, electrocardiogram, echocardiogram and ophthalmologic assessments), no new safety issues are identified based on the provided data.

No new safety issues emerged from intrinsic and extrinsic factors.

No specific trends were observed, and no new safety concerns are identified with concomitant administration of selumetinib with any of the medications commonly prescribed for patients with NF1-PN.

Post-marketing

No new data on the important identified and potential risks or on the missing information that would change the characteristics of the safety concerns were identified post-marketing.

2.7.2. Conclusions on clinical safety

The safety data from the KOMET study indicates that treatment with selumetinib has a manageable safety and tolerability profile in adults with NF1 who have symptomatic, inoperable PN. Except for the new ADRs constipation and rashes acneiform, the safety profile is consistent with the existing safety profile of the paediatric population.

2.7.3. PSUR cycle

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.

2.8. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 4.1 with the following content:

Safety concerns

Table 40: 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)

Pharmacovigilance plan

Table 41: 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 2023 Q3 2024 Q3 2025 Q3 2026 Q3 2027 Q3 2025 31 March 2029

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

Risk minimisation measures

Table 42: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Left ventricular ejection fraction reduction	Routine risk minimisation measures for LVEF reduction: SmPC sections 4.2, 4.4, 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Physeal dysplasia	None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Ocular toxicity	Routine risk minimisation measures for ocular toxicity: SmPC sections 4.2, 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Myopathy	Routine risk minimisation measures for myopathy: None. Routine risk minimisation measure for increases in CPK: SmPC section 4.8.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures for hepatotoxicity: None. Routine risk minimisation measures for elevations in ALT and AST: SmPC sections 4.4, 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Long-term exposure (including long-term safety data on developmental toxicity in children)	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: SPRINT Phase II study long-term follow-up Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)

No changes were made to the safety concerns, pharmacovigilance plan and risk minimisation measures as a result of this extension of indication.

2.9. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template.

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

Changes proposed to the leaflet as a result of the revised indication were minimal and did not affect readability.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

*Koselugo as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in **adult and** paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and **older**.*

3.1.2. Available therapies and unmet medical need

There is currently one systemic treatment option approved for patients with NF1 PN: Ezmekly (mirdametinib), an oral selective MEK inhibitor, approved in the EU in 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 Application is supported by an ongoing, Multicentre, International Study with a Parallel, Randomized, Double-blind, Placebo-controlled, Two-arm Design to Assess the Efficacy and Safety of Selumetinib in Adult Participants with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET) Phase III study.

Supportive data come from an open label Phase I study with 2 independent cohorts (adults and paediatrics) to assess the safety, tolerability, PK, and clinical efficacy of selumetinib in Chinese participants with NF1 and inoperable PN (Study 11).

3.2. Favourable effects

A total of 145 participants (selumetinib: 71; placebo: 74) were randomized in the main study and received at least 1 dose of study intervention.

The observed Objective Response Rate (ORR) on the target tumour volume using volumetric MRI analysis determined by ICR (per REiNS criteria) in the selumetinib group was 19.7% (95% CI = 11.2, 30.9) versus 5.4%, (95% CI = 1.5, 13.3) in the placebo group, all of them being confirmed partial response (i.e. volume decrease ≥ 20% confirmed within 3 to 6 months after first response).No participant had a complete response. The difference was statistically significant (2-sided p = 0.0112).

- 5 (7%) participants had an unconfirmed PR in the selumetinib group versus 8 (10.8%) in the placebo arm
- One (1.4%) participant had a progressive disease (volume increase ≥20%) in the selumetinib group versus 5 (6.8%) in the placebo arm.

The median time to response at DCO2 was 3.73 months (95% CI = 3.61, 11.07), among the 14 responders reported in the Selumetinib arm, 9 (64.3%) had a response sustained for more than 12 months at final analysis.

3.3. Uncertainties and limitations about favourable effects

It is noticeable that the ORR in the adult population is lower than the one observed with selumetinib in the paediatric population (SPRINT) (around 44%) when analysed by Independent Central Review.

However, this variation is the first extension of indication in NF1 associated PN to be based on a phase III trial which incorporated a randomised phase. Despite the lower observed response rate, a statistically significant effect was observed versus placebo on response per REiNS criteria. An AHEG consultation was conducted at the time of Koselugo initial MAA (see EPAR) which considered plausible that a decrease of PN volume is associated with a decrease in symptoms/morbidity.

3.4. Unfavourable effects

The safety profile of selumetinib in the KOMET study performed in adult patients is consistent with the existing safety profile of selumetinib in paediatric patients

The most frequently reported treatment-related events during the on-selumetinib Period were consistent with the events assessed as treatment-related during the Randomized Period and included dermatitis acneiform, blood creatine phosphokinase increased, and paronychia.

Except for the new ADR constipation and rashes acneiform, the ADRs reported in the KOMET study related to selumetinib are consistent with the ADRs reported in paediatric patients.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 43: Effects Table for KOMET

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR per REiNS criteria	Volume decrease ≥ 20% confirmed within 3 to 6 months after first response	% (95% CI)	19.7 (11.2, 30.9)	5.4 (1.5, 13.3)	Placebo controlled study Independent review Primary endpoint	KOMET
	Difference in ORR	%	14,3 p value 0.0112			
Time to response	Median TTR	Month (95% CI)	3.73 (3.61, 11.07)	ND	Descriptive only, limited number of responders	
Duration of response	Median DOR	Month (95% CI)	Not reached (11,5; NE)	ND		
	DOR rate at 12 months	%	64,3	ND		
Unfavourable Effects: Most common Grade 3 or higher AEs						
Any AE of CTCAE Grade 3 or higher	Number of patients	N (%)	23 (32.4)	13 (17.6)	Placebo controlled study	KOMET

Any ADR	experiencing a given AE		70 (98.6)	46 (62.2)		
Any ADR Grade 3 or higher			12 (16.9)	1 (1.4)		
Any ADR leading to discontinuation of study intervention			2 (2.8)	1 (1.4)		
Any ADR leading to dose modification			19 (26.8)	4 (5.4)		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Neurofibromatosis type 1 (NF1) is a rare disease caused by mutations in the NF1 tumour suppressor gene. NF1-related benign tumours, such as plexiform neurofibromas (PN), can cause significant morbidity. When NF1 patients have symptomatic PNs, surgical resection can be difficult to perform.

The pivotal study, KOMET was a phase III, multi-centre randomised double blinded placebo controlled study that aimed to evaluate the efficacy, safety and PK, of selumetinib in adult participants with NF1 and inoperable PN with existing PN-related morbidity at enrolment.

In the interim analysis the most relevant effect was the statistically significant difference in the ORR on the target tumour volume (per REiNS criteria).

At the Final Analysis the median duration of response remained unreached and of 14 participants with confirmed responses at the Primary Analysis, all remained responder for ≥6-month response, and 64.3% for ≥12 months.

It is noticeable that the ORR in the adult population is lower than the one observed with selumetinib in the paediatric population (SPRINT) (around 44%) when analysed by Independent Central Review.

However, this variation is the first extension of indication in NF1 associated PN to be based on a phase III trial which incorporated a randomised phase. Despite the lower observed response rate, a statistically significant effect was observed versus placebo on response per REiNS criteria. An AHEG consultation was conducted at the time of Koselugo initial MAA (see EPAR) which considered plausible that a decrease of PN volume is associated with a decrease in symptoms/morbidity.

The effect of selumetinib on the volume and growth rate of PN in adult participants with NF1 has been established and positive trend favouring selumetinib was also observed in PAINS-pNF chronic target PN pain intensity (key secondary endpoints)) at the end of the placebo period in patients receiving selumetinib and also in patients who switched for placebo to selumetinib in the open label part of the study.

The safety profile of selumetinib in the KOMET study performed in adult patients is consistent with the safety data assessed during the MA process and from post-marketing monitoring. .

3.7.2. Balance of benefits and risks

The most relevant effect was the statistically significant difference in the ORR on the target tumour volume using volumetric MRI analysis determined by Independent Central Review (per REiNS criteria) in the selumetinib group versus the placebo group. A positive trend favouring selumetinib was also observed in PAINS-pNF chronic target PN pain intensity (key secondary endpoints) at the end of the placebo period in patients receiving selumetinib and in patients who switched for placebo to selumetinib in the open label part of the study.

The safety profile of selumetinib in the KOMET study performed in adult patients is consistent with the safety data assessed during the MA process and from post-marketing monitoring

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall B/R of Koselugo is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication for KOSELUGO to include treatment of adults based on results from study D134BC00001 (KOMET). This is a phase III, multicentre, international study with a parallel, randomised, double-blind, placebo-controlled, 2 arm design that assesses efficacy and safety of selumetinib in adult participants with NF1 who have Symptomatic Inoperable Plexiform Neurofibromas. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial changes to the SmPC.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIB and to the Risk Management Plan are recommended.

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

- **Risk management plan (RMP)**

The 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.

In addition, 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.

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. 847/200. See appendix 1.

Additional market protection

The request for one year of market protection for a new indication was withdrawn by the MAH during the procedure.