22 April 2021
EMA/549867/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Koselugo

International non-proprietary name: selumetinib

Procedure No. EMEA/H/C/005244/0000

Note

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

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List of abbreviations

ADI	Acceptable Daily Intake
ADR(s)	Adverse drug reaction(s)
AE(s)	Adverse event(s)
AESI	Adverse events of special interest
AHI	Apnoea-Hypopnoea Index
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine triphosphate
AUC	Area under the plasma concentration-time curve
AUC0-6	Area under the plasma concentration-time curve from time zero to 6 hours
AUC0-12	Area under the plasma concentration-time curve from time zero to 12 hours
AUC0-24	Area under the plasma concentration-time curve from time zero to 24 hours
AUClast	Area under the plasma concentration-time curve from time zero to last time of quantifiable concentration
Aw	Water Activity
BCRP	Breast cancer resistant protein
BCS	Biopharmaceutics Classification System
BID	Twice daily
BOR	Best objective response
BSA	Body surface area
CCHMC	Cincinnati Children's Hospital Medical Center
CFU	Colony Forming Units
CHMP	Committee for Human Medicinal Products
CHOP	Children’s Hospital of Philadelphia
CI	Confidence interval
Cmax	Maximum plasma concentration
CMT	Clinically meaningful threshold
CNMC	Children’s National Medical Center
COA	Clinical outcome assessment
COMP	Committee for Orphan Medicinal Products
CPK	Creatine phosphokinase
cPR	Confirmed partial response
CR	Complete response
CQA	Critical Quality Attribute
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV%	Coefficient of variation
CYP	Cytochrome p450

DCO	Data cut-off
DLT	Dose-limiting toxicity
DoR	Duration of response
DVQ	Dysfunctional Voiding Questionnaire
EAP	Early Access Programme
ECG	Electrocardiogram
ECHO	Echocardiogram
EFD	Embryofoetal development
EIPNA	N-nitrosoethylisopropylamine
EMA	European Medicines Agency
ERK	Extracellular signal-regulated kinase
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FED	Factorial Experimental Design
FEV0.75	Forced expiratory volume in 0.75 seconds
FEV1	Forced expiratory volume in 1 second
GC	Gas Chromatography
gCV	Geometric coefficient of variation
GCP	Good Clinical Practice
GD	Gestation day
GI	Gastrointestinal
GIC	Global Impression of Change
GTP	Guanosine 5'-triphosphate
GVP	Good Pharmacovigilance Practice
HDPE	High-density polyethylene
hERG	Human Ether-a-go-go-Related Gene
HRQoL	Health-related quality of life
IC	Ion chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
ICR	Independent central review
IPR	Individual patient review
IR	Infrared
IR	Immediate release
KBE	Key Binding Element
KF	Karl Fischer titration
LC	Liquid chromatography
LC-UV	Liquid chromatography-ultraviolet
LDPE	Low Density Polyethylene
LOAEL	Lowest observed adverse effect level
LVEF	Left ventricular ejection fraction

MAA	Marketing Authorisation Application
MATE	Multidrug and toxin extrusion transporter
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
Min	Minimum
MMRM	Mixed model repeated measures
MMT	Manual muscle test
MO	Major Objection
MPNST	Malignant peripheral nerve sheath tumours
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
MTD	Maximum tolerated dose
6-MWT	6-minute walk test
NA	Not available/Not applicable
NCI	National Cancer Institute
NDA	New Drug Application
NDMA	N-Nitrosodimethylamine
NF1	Neurofibromatosis type 1
NI-PASS	Non-interventional Post Authorisation Safety Study
NMT	Not more than
NOAEL	No observed adverse effect level
NOEL	No observed effect level
NRS-11	Numerical rating scale-11 (pain measurement)
NSCLC	Non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
ORR	Objective response rate
PAR	Proven Acceptable Range
PBMC	Peripheral blood mononuclear cells
PDCO	Paediatric committee
PDE	Permitted Daily Exposure
PedsQL	Pediatric Quality of Life Inventory
Ph. Eur.	European Pharmacopoeia
PII	Pain interference index
PIP	Paediatric Investigation Plan
PRO	Patient reported outcome
PROMIS	Patient-reported outcomes measurement information system
PFS	Progression-free survival
QC	Quality Control
QSAR	Quantitative Structure-Activity Relationship
QTPP	Quality target product profile
QWP	Quality Working Party

REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
RH	Relative Humidity
SM	Starting Material
SmPC	Summary of Product Characteristics
THF	Tetrahydrofuran
TPGS	Vitamin E polyethylene glycol succinate
TTC	Threshold of toxicological concern
UDU	Uniformity of Dosage Units
UGT	Uridine diphosphate-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
UV	Ultraviolet
WHO	World Health Organization
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 6 March 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Koselugo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2018.

Koselugo, was designated as an orphan medicinal product EU/3/18/2050 on 31 July 2018 in the following condition: treatment of neurofibromatosis type 1 (NF1).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Koselugo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/koselugo.

The applicant applied for the following indication: Koselugo is indicated for the treatment of paediatric patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0279/2019 was not yet completed as some measures were deferred.

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 applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Conditional marketing authorisation

The applicant applied for a full marketing authorisation, but during the assessment, in response to CHMP concerns on the comprehensiveness of the data, requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of the above mentioned

Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance selumetinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
13 December 2018	EMEA/H/SA/2400/2/2018/PA/PED/III	Dr André Elferink, Dr Daniel O'Connor
14 November 2019	EMEA/H/SA/2400/2/FU/1/2019/PA/III	Dr André Elferink, Dr Andreas Kirisits

The applicant received Scientific Advice for the development of selumetinib for treatment of neurofibromatosis type 1 related symptomatic, inoperable plexiform neurofibromas. The Scientific Advice pertained to the following Non-Clinical and Clinical aspects:

- Non-clinical evidence generation: general strategy and carcinogenicity study plans to support MAA in the paediatric population
- Food-effect study
- Pivotal evidence to demonstrate safety and efficacy in the target population in the context of an envisaged conditional marketing authorisation application: single pivotal study strategy, use of external historic control data, matching methodology, expected clinical safety database, GCP compliance
- Post-approval evidence generation plans to generate comprehensive evidence base after a potential Conditional Marketing Authorisation: risk-mitigation plans, long-term follow-up of single pivotal study and proposed post authorisation safety study
- Evidence to confirm Significant Benefit in the context of the Orphan Designation

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Paula Boudewina van Hennik

The application was received by the EMA on	6 March 2020
The procedure started on	26 March 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	15 June 2020

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	29 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	23 July 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	02 February 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 February 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 February 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	02 March 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	21 March 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Koselugo on	22 April 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for Koselugo (selumetinib) is:

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

2.1.2. Epidemiology

NF1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene (17q11.2), which encodes the tumour suppressor protein neurofibromin 1. Studies that included both adult and paediatric populations reported prevalence estimates of NF1 between 20 per 100000 and 24 per 100000 persons (Huson et al. 1989; Poyhonen et al. 2000; Evans et al. 2010; Kallionpää et al. 2018), whereas, studies focusing only on paediatric populations or adolescents found slightly higher prevalence estimates ranging from 18 per 100000 to 34 per 100000 persons (Poyhonen et al. 2000; Lammert et al. 2005; McKeever et al. 2008). Approximately half of NF1 cases are familial, with penetrance being 100%, and the remainder are the result of de novo (spontaneous) mutations (Evans et al. 2010).

2.1.3. Aetiology and pathogenesis

Neurofibromin 1 is a guanosine 5' triphosphate (GTP)ase activating protein that promotes the conversion of active RasGTP 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).

Pathophysiology of NF1-related plexiform neurofibromas (PNs)

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

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

2.1.4. Clinical presentation, diagnosis, prognosis

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.

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 reported 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).

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.

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).

The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration recommends the following patient-reported outcome (PRO) instruments to assess pain and physical functioning in NF clinical trials:

- the Numerical rating scale-11 (NRS-11) instrument for the (self-reported) assessment of pain intensity in NF patients aged ≥8 years (Wolters et al. 2013; Wolters et al. 2016);
- the pain interference index (PII) instrument for the assessment of pain interference in NF1 patients, self-reported in patients aged 6-24 years and parent-reported for patients aged 6-18 years (Wolters et al. 2016); and
- the Patient-reported outcomes measurement information system (PROMIS) instrument to measure mobility and upper extremity function, self-reported in patients aged 8-17 years and parent-reported for patients aged 5-17 years (Wolters et al. 2016).

Association of PN volume changes and development of clinical morbidities

Given the rarity of the disorder, there is little available literature that documents the clinical course and impact of PN-related clinical complications. Recently, the first detailed report following the change in PN growth and development of PN-related clinical symptoms over an extensive time period (at least 7 years of clinical data in each patient, 41 patients included) was published (Gross et al. 2018). It was reported that the majority of PN had already resulted in symptoms at the baseline assessment, where the median patient age was 8 years old. Compared with PN that did not cause symptoms/clinical complications, PN resulting in pain and motor dysfunction tended to be larger in volume at baseline, consistent with an earlier report (Nguyen et al. 2011). There was a relationship between PN with faster growth rates and increases in analgesic use, compared with those PN with slower growth rates. For non-motor symptoms, such as visual or bowel/bladder dysfunction, smaller PN could cause significant clinical impact depending on their location and a slower growth rate may also result in clinical deterioration.

No stable or growing PN had resolution of functional impairment between baseline and maximum assessments.

The overwhelming trend in patients with stable or growing PN is that their symptoms remain stable or worsen over time.

NF1 is associated with an 8- to 15-year reduction in average life expectancy in both men and women, primarily due to malignant neoplasms and cardiovascular causes (Evans et al. 2011; Uusitalo et al. 2015).

2.1.5. Management

Currently, the only available options to treat and manage NF1 are pain management and surgical excision to remove as much of the PN as possible. However, for many patients, surgery is not a viable option as most PN are not amenable to complete resection due to encasement of, or close proximity to, vital structures (Korf. 1999; Needle et al 1997; Packer et al 2002). Furthermore, complete resection is difficult to achieve, with a high risk of iatrogenic injury to related nerves and surrounding soft tissues and haemorrhage due to the invasiveness or high vascularity of the PN (Canavese and Krajbich. 2011). Following subtotal or partial PN resection, 18% of patients experienced permanent surgical complications, including speech abnormalities, nerve palsies, and pain, and 55% of patients experienced PN regrowth (Prada et al 2012). Furthermore, incompletely resected PN tend to regrow after surgery (Canavese and Krajbich. 2011).

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 Adenosine triphosphate (ATP). MEK1/2 are critical components of the RAS-regulated, RAF-MEK-ERK pathway which is frequently activated in human cancer. The pathway is activated by an array of receptor types including receptor tyrosine kinases, G protein-coupled receptors and cytokine receptors. MEK1/2 are dual specificity kinases that activate extracellular signal-regulated kinase (ERK)1/2 by phosphorylating them at conserved threonine and tyrosine residues in their activation loop. MEK1 and MEK2 show high (79%) amino acid identity and are considered equally able to phosphorylate and activate their substrates ERK1/2. In contrast to the exclusive substrate specificity of MEK1/2 for ERK1/2, hundreds of proteins have been identified as ERK substrates and this explains how the RAF-MEK-ERK pathway can influence many cellular processes including tumour cell proliferation, and survival. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.

Of specific relevance to this application, the causative genetic alterations in NF1 are mutations or microdeletions in the tumour suppressor gene NF1 which encodes the protein neurofibromin-1. Neurofibromin-1 contains a GAP (GTPase activating protein) related domain (GAD) whose normal function is to promote the inactivation of RAS through enhancing its GTPase activity. This results in activation of the RAF-MEK-ERK pathway and provides the rationale for the use of selumetinib for the proposed indication.

Further to the review of the application, the CHMP agreed to the following indication:

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

Treatment with Koselugo should be initiated by a physician experienced in the diagnosis and the treatment of patients with NF1 related tumours.

The recommended dose of Koselugo is 25 mg/m2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours).

Dosing is individualised based on BSA (mg/m^2) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of Koselugo capsules can be combined to attain the desired dose (Table 1).

Table 1: Recommended dosage based on body surface area

Body surface area (BSA)[a]	Recommended dosage
0.55 – 0.69 m^2	20 mg in the morning and 10 mg in the evening

Body surface area (BSA) [a]	Recommended dosage
0.70 – 0.89 m^2	20 mg twice daily
0.90 – 1.09 m^2	25 mg twice daily
1.10 – 1.29 m^2	30 mg twice daily
1.30 – 1.49 m^2	35 mg twice daily
1.50 – 1.69 m^2	40 mg twice daily
1.70 – 1.89 m^2	45 mg twice daily
≥ 1.90 m^2	50 mg twice daily

[a] The recommended dosage for patients with a BSA less than 0.55 m^2 has not been established.

Treatment with Koselugo should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. There is limited data in patients older than 18, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician. However, start of treatment with Koselugo in adults is not appropriate.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that:

- Based on the available information, it was considered uncertain whether the limited data package (both in terms of study design and size) would enable to conclude on a positive benefit/risk and that thereby the unmet medical need would be fulfilled.
- The clinical relevance of the observed activity was considered uncertain given the large heterogeneity in the natural course of the disease in the context of a single arm trial and uncertainty regarding the validity of the provided external controls. Therefore, the CHMP were of the opinion that the data presented at the time of the request did not justify per se an accelerated assessment (CHMP conclusion on 12 December 2019).

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above mentioned Regulation, based on the following criteria:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data:
  - Efficacy and safety data from a second data cut-off (DCO) (proposed DCO: 31 March 2021) of the pivotal SPRINT Phase II Stratum 1 that will provide 2 years and 9 months of further data. AstraZeneca proposes to provide long-term efficacy; PN response (DOR and PFS) based on NCI central analysis, and clinical outcome measures (COA) (pain, motor, and HRQoL) as well as additional long-term safety data. Long-term follow-up data are collected on patients for at least 7 years from initiation of selumetinib treatment.
  - Efficacy and safety data from a second DCO (27 February 2021) of SPRINT Phase I, that will provide a further 2 years 8 months data from the MAA submission DCO June 2018. The data presented for SPRINT Phase I will include long-term efficacy; PN response (DOR and PFS), and safety data as first patient was enrolled in 2011 and last patient was enrolled in 2014.
- Unmet medical needs will be addressed, as there are no medicinal products authorised in Europe for the treatment of NF1 symptomatic, inoperable PN in paediatric patients aged 3 years and above.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 10 and 25 mg of selumetinib (as hydrogen sulfate) as active substance.

Other ingredients are:

Capsule content
Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol succinate).

Koselugo 10 mg hard capsules

Capsule shell
Hypromellose (E464)
Carrageenan (E407)
Potassium chloride (E508)
Titanium dioxide (E171)
Carnauba wax (E903)

Printing ink
Shellac glaze, standard (E904)
Iron oxide black (E172)
Propylene glycol (E1520)
Ammonium hydroxide (E527)

Koselugo 25 mg hard capsules

Capsule shell
Hypromellose (E464)
Carrageenan (E407)
Potassium chloride (E508)
Titanium dioxide (E171)
Indigo carmine aluminium lake (E132)
Iron oxide yellow (E172)
Carnauba wax (E903)
Maize starch

Printing ink
Iron oxide red (E172)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132)
Carnauba wax (E903)
Shellac, standard (E904)
Glyceryl monooleate

The product is available in high-density polyethylene (HDPE) plastic bottle with child-resistant polypropylene closure (10 mg: white closure, 25 mg: blue closure) and silica gel desiccant, containing 60 hard capsules, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of selumetinib hyd-sulfate is 5-[(4-bromo-2-chlorophenyl)amino]-4-fluoro-6-[(2-hydroxyethoxy)carbamoyl]-1-methyl-1*H*-benzimidazol-3-ium hydrogen sulfate corresponding to the

molecular formula $C_{17}H_{17}BrClFN_4O_7S$ (free base: $C_{17}H_{15}BrClFN_4O_3$. It has a relative molecular mass of 555.76 (free base: 457.68) and the following structure:

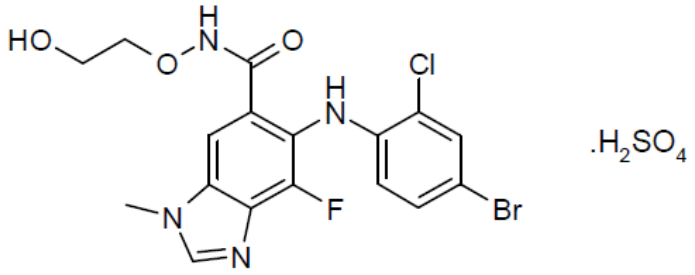


Figure 1: Active substance structure

The chemical structure of selumetinib hyd-sulfate was elucidated by a combination of mass spectrometry (MS), proton (^1H), carbon (^{13}C) and fluorine (^{19}F) nuclear magnetic resonance (NMR) spectroscopy, infrared spectroscopy (IR) and ion chromatography (IC). In addition, the 1:1 salt stoichiometry of selumetinib hyd-sulfate has been confirmed by single crystal X-ray diffraction (XRD).

The active substance does not exhibit stereoisomerism.

Selumetinib hyd-sulfate is a non-hygroscopic white to yellow crystalline powder. Selumetinib has low solubility and low permeability as defined by the Biopharmaceutics Classification System (BCS) and thus is a BCS Class 4 compound. It is practically insoluble in water, slightly soluble in ethanol and acetonitrile.

Selumetinib hyd-sulfate is monomorphic and all batches produced using the proposed manufacturing process have exhibited consistent X-ray powder diffraction patterns (XRPD). Extensive solid-state investigations, including polymorph screening, identified a number of solvates but no additional crystalline non-solvated forms of selumetinib hyd-sulfate. The hyd-sulfate polymorph is controlled in the specifications and monitored on stability.

Manufacture, characterisation and process controls

The active substance is synthesized in two main steps with isolated intermediates and one salification step, using commercially available well defined starting materials (SM) with acceptable specifications. The selection of starting materials has been justified and considered appropriate, since upstream materials would not ensure a higher quality of the active substance. The manufacturer, synthesis process, specifications, analytical methods have been provided. The specifications for impurities in the starting materials, the level of purge and the control strategy were discussed during the review (see major objection discussed below). The specifications and the in-process controls are presented and justified. 1

Several PARs have been established. It has been clarified that these are interpreted as defined in ICH Q8 and do not constitute a design space. Target values for the parameters have also been defined.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance presents a quantitative structure-activity relationship (QSAR) alert, however it is negative in vitro (Ames negative).

A risk assessment of the synthesis route with regard to mutagenic impurities was performed in line with ICH M7 using two (Q)SAR prediction methodologies complementing each other. It included starting materials, intermediates, reagents, synthesis and degradation impurities. Several alerting structures (class 1, 2, and 3) were identified. Their control relies upon an understanding of the impurity purging capabilities of the manufacturing process.

All Class 1, 2 and 3 mutagenic impurities are controlled below the threshold of toxicological concern (TTC) limit using either option 3 or 4 of ICH M7. Calculated purge factors and purge ratios were used to justify the Options 3 or 4 control strategy. In the calculation of required purge, the applicant applied an acceptable daily intake (ADI) of 10µg/day, for treatment duration of less than 10 years without any justification. This was questioned during the evaluation since, according to the SmPC, the product is indicated for the treatment of paediatric patients aged 3 years and above, which suggests that the product can be used for a longer time period than 10 years. In addition, when multiple class 2 or 3 impurities are specified, total mutagenic impurities should be limited to the ADI for multiple impurities according to ICH M7 (5µg/day for the sum of all impurities), even more so as multiple impurities are likely to have same mechanism (e.g. same structural alert). Considering this, a major objection asking the applicant to revise the control strategy for mutagenic impurities was raised.

In addition, the available fate and purge data did not allow to conclude that the proposed specifications for class 2 and 3 mutagenic impurities in upstream process are sufficient to ensure the levels of impurities in the active substance are below 30% of the acceptable limit and therefore to support the Option 3 control strategy. Supportive analytical results or an appropriate control strategy (specifications at the TTC level for multiple impurities in the drug substance) were requested as part of the major objection.

In his response, the applicant provided analytical data and argued that a <10 years dose duration represented the anticipated duration for the treatment of the majority of patients. Only a subset of patients would be expected to be treated for more than 10 years; dosing extending the full theoretical treatment period from 3 to 18 years (15 years duration), although theoretically possible, will be highly unlikely. In fact, median actual treatment in the clinical studies was below 5 years. Therefore, in line with the exception in ICH M7, the application of a limit of 100 ppm calculated on a < 10µg/day for a <10 years dosing duration and 100 mg selumetinib dose was considered justified.

The applicant indicated that for all impurities, the purge ratio is appropriately high, reaffirming his position that all such impurities are effectively controlled in accordance with ICH M7. It has been sufficiently justified that mutagenic impurities are purged far below 30% of the acceptable limit according to ICH M7.

A risk assessment for elemental impurities in accordance to ICH Q3D was performed. Intentionally added metals and common environmental metals (Class 1 and 2A) were considered. Applying a worst case posology (maximum daily dose of 100mg), the maximum permitted concentration was determined. Five batches of active substance were analysed and levels are below 30% of the PDE calculated with option 2B.

Solvents used in the process have been discussed and appropriate control has been demonstrated.

The applicant stated that a risk assessment for the presence of nitrosamines in selumetinib hyd-sulfate had been conducted and a negligible risk of the presence of nitrosamines was identified. It was claimed that nitrosamines that could be generated during selumetinib hyd-sulfate synthesis would purge to a level below the analytical limit of detection in the active substance. However, the underlying data were

not provided and the finished product was not covered in the risk assessment. This was not considered sufficient (see major objection discussion under finished product specification).

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. An overview of the development of the synthetic process has been presented.

Early studies used selumetinib free base as the active substance, which was manufactured by a route that differed significantly from the route now proposed to manufacture selumetinb hyd-sulfate. The selumetinib free base route was a linear synthesis via step wise halogenation of the aniline moiety. This route was superseded by the convergent selumetinib hyd-sulfate routes, which introduce the aniline moiety with the requisite chloro and bromo subsitituents already in place, being more efficient, safer to operate, more environmentally benign and producting better quality active substance.

The synthetic route for the manufacture of selumetinib hyd-sulfate changed in early development from the first generation to the second generation route, the main changes being made in order to improve the impurity profile and manufacturability. Changes introduced have been presented in sufficient detail and have been justified. The first generation route, was used to manufacture two batches that have been used in toxicological studies. The majority of active substance batches have been manufactured using the intended commercial manufacturing process (second generation route). These batches have been used in clinical and pivotal stability studies.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double low-density polyethylene (LDPE) bags, within a rigid outer container. The rigid outer container provides light and physical protection during storage and transit. The primary packaging complies with EC regulation 10/2011 EC 10/2011 as amended.

Specification

The active substance specification includes tests for description (visual), identification (IR, XPRD), assay (LC), organic impurities (LC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), and particle size (laser diffraction).

2The proposed acceptance criteria for specified organic impurities have been derived following principles of ICH and are based on a combination of process capability, toxicological qualification, available stability data and batch data from pilot and commercial scale manufactures.

Specified impurities have been qualified by toxicological and clinical studies . All other organic impurities are controlled by the individual unspecified impurity clause.

The control strategy for residual solvents has been justified and is acceptable.

As indicated above, selumetinib is a BCS Class 4 compound. Particle size is included in the specification.

In accordance with the principles of ICH M7, the likelihood of identified Class 1, 2 and 3 impurities being present in selumetinib hyd-sulfate has been assessed through process data and the use of calculated purge factors (see discussion above). All Class 1, 2 and 3 impurities are controlled under either option 3 or 4 of ICH M7.

The absence for a specific specification test for counter ion content has been justified on the basis of the combination of assay and identification, using two specific identity methods: IR and XPRD, which provide assurance for selumetinib hyd-sulfate 1:1 salt stoichiometric form.

The control of elemental species used in the selumetinib hyd-sulfate manufacturing process to less than the ICH Q3D option 2B limit upstream of the active substance has been justified. Therefore, it is not necessary to include a specification for them at the level of the active substance.

The absence of a test for microbial limit has been justified, based on the high microbiological quality of selumetinib hyd-sulfate batches and the low potential for microbial growth. The potential for microbial contamination in selumetinib hyd-sulfate has been justified to be very low. This was supported by microbial testing performed during stability and development scale batches which confirmed that all batches of selumetinib hyd-sulfate have very low viable counts (<10 cfu/g).

The water content of selumetinib hyd-sulfate (and hence potential for microbial growth on storage) is controlled in the manufacturing process to very low levels .

A mould challenge test has been performed on selumetinib hyd-sulfate and demonstrates that the active substance does not support mould growth. In addition, it has been established that selumetinib hyd-sulfate does not support microbial growth since the water activity (Aw) of batches are below the minimum level required for microbial growth (Aw 0.60).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding selumetinib reference standard for identity and assay testing has been presented.

Batch analysis data for an extensive number of batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer and three primary pilot scale stability batches from another manufacturer, stored for up to 60 months under long term conditions (25°C / 60% RH) and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one primary stability pilot scale batch.

Batches were packed in double polyethene bags in a foil-lined fibreboard drum. The container closure for stability studies is representative of the commercial container closure.

The following parameters were tested: description, identification (by XRPD for primary stability; IR for commercial stability both providing discrimination for changes in solid state form), assay, organic impurities and water content. Microbiological quality testing was performed periodically for information only. The analytical methods used were the same as for release and were stability indicating.

Particle size testing was not included in the primary stability study since the particle size of selumetinib hyd-sulfate has been shown to be unaffected when stored in double polyethene bags in a foil-lined drum at 25°C/60% RH during development.

No significant change was observed in any of the parameters tested in samples stored for up to 72 months at long-term (25°C /60% RH) and for 6 months at accelerated (40°C /75% RH) storage conditions. All active substance batches complied with the active substance specification and support the proposed retest period.

No significant change to description, identification, assay, water content or microbiological quality was observed for the selumetinib hyd-sulfate pilot scale batch exposed to the photostability conditions. However, the level of an unspecified organic impurity showed a significant change failing the

specification limit. The photostability study indicates that, to ensure the quality of the active substance during storage, selumetinib hyd-sulfate should be stored protected from light. The proposed container has been shown to provide suitable protection from light.

The stability indicating character of the analytical method for assay and impurities has been adequately demonstrated via forced degradation studies in solid and in solution phase. These included: thermal stress (60°C, solid state), hydrolytic degradation (60°C/80%RH, 50°C /75%RH, 60°C/75%RH, 70°C/75% RH, photostability (solid state), acid and base (pH 1, pH 7, and pH 13 solution), oxidative hydrolysis and metal ions.

The main degradation impurities under the different stress conditions have been described The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored below 30°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Selumetinib capsules are opaque two-piece hard hypromellose capsules sealed with a clear hypromellose band. They are presented as two strengths:

- 10 mg capsules presented as white capsules marked with 'SEL 10' printed in black ink.
- 25 mg capsules presented as blue capsules marked with 'SEL 25' printed in black ink.

The capsules are size 4 (14.3 x 5.3 mm). As described in the SmPC, the capsules should be swallowed whole with water. The capsules should not be chewed, dissolved, or opened, because this could impair drug release and affect the absorption of selumetinib. This pharmaceutical form and its size would in principle not be considered a suitable age-appropriate formulation as proposed by the applicant as there is a risk for reduced patient compliance (treatment discontinuation) and, for younger children, a risk of choking or chewing the capsule. The CHMP raised a multidisciplinary Major Objection (MO) requesting the applicant to discuss how these aspects will be addressed in real life practice in the paediatric population and to further justify the use of the capsules in the youngest patients. Although based on clinical experience in the pivotal trial, children from the age of 3 years have been able to swallow the capsules whole (with or without proper training), these findings for a limited number of patients are not considered sufficient to conclude that the capsules are age-appropriate in general and in real-life, where it is anticipated that at least part of especially the younger children will be unable or unwilling to swallow the capsules whole as intended. However, considering the lack of available treatment for the intended indication and the high unmet medical need in this seriously debilitating condition, the capsule formulation is exceptionally accepted pending the development by the company of an alternative age-appropriate formulation as per the PIP decision for selumetinib. Nevertheless, since it is anticipated that not all children (particularly the youngest) in the indicated age range will be able or willing to swallow the capsules whole, it is considered essential that the alternative age-appropriate formulation described in the PIP becomes available as soon as possible.

First-in-patient clinical studies in adults were performed using a 100 mg suspension of selumetinib free base in sulfobutylether-beta-cyclodextrin aqueous solution prepared immediately before use. This formulation exhibited poor bioavailability due to the solubility limitations of the free base and was not progressed further.

Development of a salt of selumetinib was pursued. The hyd-sulfate salt of selumetinib was selected for development as it improves the bioavailability as demonstrated in the relative bioavailability study; Study 5 (D1532C00005).

Selumetinib hyd-sulfate was progressed to formulation development studies with a target of delivering selumetinib from an oral, immediate release (IR) solid dosage form.

A Quality Target Product Profile (QTPP) was defined which framed the pharmaceutical development program. The primary aim of the QTPP was to develop an age appropriate formulation which met the needs of the paediatric patient population, while ensuring establishment of a robust formulation and manufacturing process which delivers a product which consistently meets the critical quality attributes and exhibits good chemical and physical stability throughout the product shelf-life.

The QTTP was to develop an oral, immediate release solid dosage swallable by 3-18 years old patients that provides appropriate dosing flexibility for patients based on BSA. Capsule strengths are to be differentiated through different capsule colours and different bottle closure colours for each strength. The selected manufacturing process and packing configuration should ensure chemical and physical stability throughout the product shelf life. Physical stability is necessary to maintain the bioavailability advantage.

Pharmaceutical development activities initially focused on the development of an IR tablet, however manufacturability issues and long term excipient incompatibility precluded further tablet formulation development. Capsule formulations containing a powder blend were also found to be unfeasible, encountering issues of manufacturability and excipient compatibility analogous with those observed during initial tablet development. A screen of lipidic excipients led to the selection of TPGS vitamin E polyethylene glycol succinate (hereinafter referred to as TPGS- Tocopheryl Polyethylene Glycol Succinate) for further assessment.

During this assessment, an encapsulated suspension of selumetinib hyd-sulfate in a solid matrix of TPGS in a sealed two-piece, hard hypromellose capsule shell (size 4) was found to preserve the stability of the hyd-sulfate salt and provide the manufacturability required for a commercial product. A dog study (0571KD) demonstrated the good oral bioavailability of selumetinib when presented as an encapsulated dispersion of the hyd-sulfate salt in a TPGS matrix.

A comprehensive assessment of the selumetinib capsule formulation was performed to determine formulation robustness prior to further clinical development. The impact of selumetinib hyd sulfate drug load suspended in TPGS in capsules was evaluated. The actual drug loading of commercial capsules falls within the range assessed. this formulation design was selected for clinical and commercial development. Two strengths of the selumetinib capsule were developed, 10 and 25 mg, which support dose flexibility in the proposed indication and patient population. Both strengths are qualitatively equivalent in terms of composition, however, to maintain manufacturability and fill weight control, drug loading and fill weight was varied within the range assessed for formulation robustness. During development only minor changes were made to the capsules:

To support differentiation of the strengths and support patient compliance, the capsule shell colour differs; the 10 mg capsule is white, and the 25 mg capsule is blue.

As indicated above, selumetinib is a BCS Class 4 compound and selumetinib capsules exhibit good oral bioavailability. As discussed earlier, a particle size control limit has been included in the active substance specification. TPGS is the primary excipient present in the formulation and is included for stability purposes. During selection of the capsule shell, different types of hard hypromellose capsule shells were evaluated. The capsule shell provides a tough protective casing for the product matrix. The hypromellose two-piece shell is sealed with a clear hypromellose band at the junction of capsule body and cap. to prevent leakage of contents. On contact with aqueous media in the gastrointestinal tract,

the capsule shell disintegrates and dissolves rapidly to provide access to the TPGS matrix containing the active substance.

All excipients are well known pharmaceutical ingredients and their quality is compliant with pharmacopoeial or EC requirements (colouring agents). There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of the active substance with the excipients used in the proposed commercial formulation has been confirmed by the results of stability studies.

The potential for selumetinib hyd-sulfate to dissociate and precipitate as selumetinib free base during dissolution in vivo or upon pH shift from a low gastric pH to a higher intestinal pH was taken into consideration during formulation development and evaluation of product performance. It was demonstrated that the selumetinib capsules, exhibit pH independent dissolution throughout the dissolution timeframe.

The release profile and stages observed have been discussed. This release mechanism has been well characterised throughout development.

The dissolution method development focused on identifying a method which is clinically relevant, appropriately discriminating, and which has suitable method capability and robustness for routine application.

During formulation and process development, a suite of dissolution tests was applied to build an understanding of the product performance across a range of physiological conditions including biorelevant pH, volumes and hydrodynamics.

The method established as the commercial quality control (QC) release method for selumetinib capsules has shown appropriate level of discrimination representative of the in vivo behaviour of variants of relevant failure modes A specification which controls for complete dissolution of selumetinib is proposed as a relevant control for in vivo performance. The limit was revised during the evaluation Selumetinib capsules have demonstrated consistent in vivo product performance with respect to pharmacokinetics throughout pharmaceutical development. This has been supported by a range of relative bioavailability and clinical pharmacology studies which characterised the biopharmaceutics of selumetinib and confirmed the in vivo performance of the commercial selumetinib capsules used in the pivotal clinical study; SPRINT.

A control strategy has been established for selumetinib capsules which ensures consistent delivery of a quality product. Controls have been defined which relate to input raw materials, PARs for CPPs, and in process controls across the manufacturing process, end product testing, and packaging and storage conditions. This control strategy provides confidence in the continuous production of selumetinib capsules which meets the quality specification upon release and for the shelf-life of the product.

The commercial formulation has been used to support the pivotal clinical study in NF1; SPRINT (D1532C00057) and supportive clinical pharmacology and biopharmaceutic studies.

The primary packaging consists of a high-density polyethylene (HDPE) plastic bottle with child-resistant polypropylene closure (10 mg: white closure, 25 mg: blue closure) and silica gel desiccant, containing 60 hard capsules. The material complies with EC requirements. The bottles and closures have been tested to and comply with the child resistance requirements in CFR 1700 and would comply with ISO 8317:2015. Selumetinib capsules are packaged within a protective pack which provides stability for the shelf-life of the product under the proposed storage conditions

The risk of accidental swallowing of the desiccant capsule was also addressed. The desiccant is sufficiently visually distinguishable from the product and bears the warning' in multiple languages and also has a do not eat symbol.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process for selumetinib capsules consists of molten liquid filling into hard two-piece hypromellose capsule shells, which comprises melting of TPGS, mixing of the molten TPGS and the active substance to produce a homogeneous mixture encapsulation of the bulk molten fill material, sealing of the capsules by banding and packaging. Given the particularities of the manufacturing process, the process is considered to be a non-standard manufacturing process.

A common manufacturing process is applied to both strengths of selumetinib capsules and the commercial manufacturing process has been established at the commercial site.

A quality, risk-based approach was taken to identify key Critical Quality Attributes (CQAs) and process parameters essential for the consistent delivery of good quality product from the manufacturing process. The CQAs identified and controlled for in the finished product specification are description, identity, uniformity of dosage unit (UDU), assay, degradation products, dissolution and microbiological quality.

Establishment and maintenance of a homogeneous mixture of selumetinib hyd-sulfate and TPGS is essential for control of content uniformity throughout manufacturing and ensuring good product quality at the end of manufacture. The critical process parameters associated with this have been defined Proven acceptable ranges (PARs) have been established for these critical process parameters and provide assurance of process robustness and product quality. Relevant product CQA for each step, associated process parameters settings and ranges, and in-process controls have been defined to guarantee product quality. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The manufacturing process has been adequately validated on three full production scale batches per strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (LC/UV), assay (LC), degradation products (LC), dissolution (LC-UV), content uniformity (LC), and microbiological quality (Ph. Eur.).

Following a request from the CHMP, the applicant added a skip-lot testing for microbial limits in the finished product.

During the review a major objection (MO) was raised since no risk evaluation concerning the presence of nitrosamine impurities in the finished product has been provided. The applicant presented a risk assessment for presence of nitrosamines, evaluating the structure of selumetinib and its impurities, the presence of nitrosating agents (nitrites) in active substance and finished product, assessment of presence of secondary and tertiary amines, assessment of potential formation of nitrosamines in the capsules and the calculation of the worst case theoretical levels of nitrosamines in the finished product. The company described in detail the origin and purge calculations of the potential nitrosamines,

nitrosating agents and vulnerable amine structures. All the currently identified root causes for the presence of nitrosamines as listed in section 4 of the EMA Q&A document EMA/409815/2020 rev 2 were considered in the risk assessment process.

In the active substance synthesis nitrosamines may potentially be formed from nitrosatable amine structures and nitrosating agents present in the process. In the finished product nitrosamines may potentially be formed from nitrosatable amine structures carried over from the active substance synthesis and trace nitrites in the excipient TPGS. The worst case estimates were compared with the permitted daily exposures extracted from EMA, FDA guidance (NMDA, DIPNA, EIPNA) and for the non-referenced impurities, on TD50 in the Lhasa database. The results from the calculations indicate that despite the presence of amine impurities and nitrosating impurities, the estimated exposure levels of individual nitrosamines are below 10% of the permitted limit and the total exposure levels are below the lowest permitted level and below the 18 ng/day identified by the EMA as the default permitted level for nitrosamines.

The applicant also provided more detailed data to substantiate the estimated exposure levels for nitrosamines in order to allow assessing the origin, fate, and purge of the potential nitrosamines. The possible formation of nitrosamines was overall based on conservative assumptions. The applicant concludes that testing in the finished product is not be necessary. This is acceptable.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk assessment concluded that there is no risk. This was confirmed by ICP-MS testing of three commercially representative batches of each product strength. All elemental impurities were demonstrated to be well below the ICH Q3D limits. Therefore, elemental impurities are not included in the finished product specification. The information on the control of elemental impurities is satisfactory.

The omission of a test for water content and residual solvents in selumetinib capsules was also justified.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for identity and assay testing has been presented.

Batch analysis results are provided for 21 batches of 10 mg capsules and 55 batches of 25 mg capsules from various scales confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from three pilot scale batches of each strength of finished product stored for up to 36 months under long term (25°C / 60% RH) and intermediate (30°C/75% RH) conditions and for up to 6 months under accelerated conditions (40°C / 75% RH) according to the ICH guidelines were provided. The batches of Koselugo are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing In addition, bulk pack stability was assessed for one batch of selumetinib capsules 10 mg and two batches of selumetinib capsules 25 mg, which were stored in double low-density polyethylene bags with desiccant, inside a container/drum.

Samples were tested for description, assay, degradation products, dissolution, water content (for information only) and microbiological quality. All the tests are performed at each time point with the exception of the test for microbiological quality which is performed at the 6 month time point at the 40°C /75% RH conditions and annually at the 25°C /60% RH and 30°C /75% RH conditions.

The primary stability data generated showed little or no change in description, assay, dissolution, degradation products or microbiological quality when stored in HDPE bottles for 36 months at 25°C/60% RH and 30°C/75% RH. An increase in water content was observed for all batches. This increase is not considered significant as it has no impact on the critical quality attributes such as assay, degradation products, dissolution and microbial quality.

At accelerated conditions, the 10 mg capsules showed little or no change in description, assay, degradation products and microbiological quality. A significant decrease in dissolution was observed for all batches of capsules and the dissolution failed to meet the requirements of the specification after 6 months. This observation was attributed to the melting point for TPGS (37°C -41°C). To avoid, this a temperature storage condition 'Do not store above 30°C ' has been established. Given that this phenomenon was not observed after 3 months of storage at accelerated conditions for any of the capsule strengths, it is not expected that short excursions above the temperature storage restriction will negatively impact product performance. Stability data for the 25 mg capsules showed little or no change in description, assay, degradation products, dissolution or microbiological quality.

Stability data for selumetinib capsules 10 and 25 mg stored in the bulk pack for 36 months at 25°C/60% RH showed similar results to the capsules stored in the commercial packaging. At 40°C/75% RH a decrease in dissolution was observed resulting in out of specification. As indicated above, this was expected given the melting temperature of TPGS.

Based on the available stability data, a holding time of 24 months is applied to selumetinib capsules 10 and 25 mg in the bulk pack with a product label storage condition of 'Do not store above 25°C '.

A forced degradation study of selumetinib capsules demonstrated the specificity and stability indicating nature of the LC method. Degradation was observed under thermal/humidity, acidic, basic, photolytic and oxidative conditions.

Photostability was assessed for one batch of each strength in accordance with ICH Q1B. Data showed little or no change in description, assay, dissolution, water content or microbiological quality. An increase in the level of an unspecified degradation product in the open petri dish sample was observed, but levels were below the quantitation limit. The data confirm that 10 and 25 mg capsules are light sensitive, and the level of light protection offered by the commercial pack is sufficient to prevent degradation under photolytic conditions.

An in-use stability study was also conducted to simulate patient use. Two aged batches of each capsule strength in both the 84 and 60 bottle count were used. Bottles were stored at 25°C/60% RH and 30°C/75% RH for 4 and 6 weeks for the 60 and 84 count study respectively. They were removed twice on each day of the study, their caps removed and replaced to simulate patient use. For both the 60 and 84 count study, no significant change in description, assay, degradation products, dissolution, water content or microbial quality was observed after 4 or 6 weeks respectively at 25°C/60% RH and 30°C/75% RH.

The data support an in-use period of at least 4 weeks at 25°C/60% RH and 30°C/75% RH when stored in the original bottle.

Based on available stability data, the proposed shelf-life of 3 years for selumetinib capsules 10 and 25 mg when stored in HDPE bottles with desiccant with a product label storage condition of 'Do not store above 30°C. Store in the original bottle to protect from moisture and light. Keep the bottle tightly closed', as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the procedure a multidisciplinary major objection was raised in relation to the proposed pharmaceutical form, which is not considered fully appropriate for the intended patient population (children from 3 years of age). Children of young age may not be able to swallow the capsule whole due to its size, leading to a risk for reduced patient compliance (treatment discontinuation) and, for younger children, a risk of choking or chewing the capsule. However, considering the unmet medical need in this seriously debilitating condition, and the data from the pivotal clinical trial indicating that patients from the age of 3 years have been able to swallow the capsules whole (with or without proper training), and that an alternative age-appropriate formulation (is currently under development by the company in line with an agreed PIP, this has been exceptionally accepted by the CHMP.

Additional major objections were raised with regards to the proposed control strategy for mutagenic impurities and the lack of a risk assessment on potential presence of nitrosamine impurities in the finished product. These major objections were adequately addressed by the applicant.

Overall, the results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Selumetinib has been evaluated in *in vitro* and *in vivo* studies that were designed to characterise the pharmacology, safety pharmacology, pharmacokinetics and toxicology of this compound. Two forms of selumetinib have been used in the nonclinical development studies: selumetinib free base and selumetinib hydrogen sulfate salt (hyd-sulfate). Initial studies were conducted using selumetinib free base. Due to the limited solubility of the selumetinib free base and the resulting low bioavailability, selumetinib hydrogen sulfate salt (hyd-sulfate) was developed and used in later studies.

2.3.2. Pharmacology

Mechanism of action

No mechanism of action studies was conducted.

Primary pharmacodynamic studies

Primary pharmacodynamics *in vitro*

<table>
<tr><th>Study</th><th>Setup</th><th>Objectives and results</th></tr>
<tr><td>Selumetinib
Kinase selectivity in biochemical enzyme assays

Pharmacology Report 01
(non GLP)
2012</td><td>MEK1

10 µM

Array Biopharma Assay, Dundee Assay: ERK1 assay for mitogen-activated protein kinase 1, Astrazeneca ELISA Assay</td><td>Objective: to determine the activity and selectivity of selumetinib (AZD6244) on the enzymatic activity of purified constitutively active MEK1 (Mitogen-Activated Protein Kinase 1) and a panel of other kinases in a series of biochemical studies

Results:
- MEK IC_{50} = 10 nM to 14 nM,
- not competitive with ATP,
- inactive, or only minimally active, against a panel of other kinases (10 µM)</td></tr>
<tr><td>Selumetinib

Selective inhibition of the MEK/ERK pathway in cultured tumour cells

Pharmacology Report 02

(non GLP)
2012</td><td>A panel of tumour cell lines, ERK phosphorylation measured by a PACE assay (Probe Assay—Chemiluminescence Enhanced).

Pathway selectivity measure in cultured cells by western blot assays</td><td>Objective: to determine the effects of AZD6244 on phosphorylation of the MEK1/2 substrates ERK1/2

Results: AZD6244 is selective for the MEK/ERK pathway and does not inhibit other cellular signalling via ERK5, mTOR, jnk or p38 kinases up to 10 µM
<table>
<tr><th>Cell line</th><th>Tumour type</th><th>IC_{50} (µM)</th><th>Cell line</th><th>Tumour type</th><th>IC_{50} (µM)</th></tr>
<tr><td>Calu-6</td><td>Lung</td><td>0.0036</td><td>Colo 205</td><td>Colorectal</td><td>0.0054</td></tr>
<tr><td>SKBR3</td><td>Breast</td><td>0.0038</td><td>MDA-MB-468</td><td>Breast</td><td>0.0099</td></tr>
<tr><td>MDA-MB-231</td><td>Breast</td><td>0.0074</td><td>Saos-2[b]</td><td>Osteosarcoma</td><td>0.0053</td></tr>
<tr><td>Calu-3</td><td>Lung</td><td>0.0018</td><td>DU-145</td><td>Prostate</td><td>0.0055</td></tr>
<tr><td>SKOV3</td><td>Ovarian</td><td>0.0408</td><td>BxPC3</td><td>Pancreatic</td><td>0.00653</td></tr>
</table></td></tr>
<tr><td>Selumetinib

N-desmethyl selumetinib

Inhibition of Erk phosphorylation in tumour cell lines

Pharmacology Report 05

(non GLP)
2019</td><td>A panel of tumour cell lines, ERK phosphorylation measured by a PACE assay (Probe Assay—Chemiluminescence Enhanced)</td><td>Objective: compare the ability of AZD6244 and the N-desmethyl metabolite of AZD6244 to inhibit the phosphorylation of ERK in seven different tumour cell lines

Results: N-desmethyl metabolite of AZD6244 is at least 3-fold more active than AZD6244
<table>
<tr><th>Cell line</th><th>AZD6244 IC_{50} nM [SE]</th><th>AZD6244 N-desmethyl metabolite IC_{50} nM [SE]</th><th>Ratio</th></tr>
<tr><td>G361</td><td>8.980 [1.873]</td><td>2.643 [0.576]</td><td>3.40</td></tr>
<tr><td>A375</td><td>9.837 [0.620]</td><td>3.353 [0.333]</td><td>2.93</td></tr>
<tr><td>A2058</td><td>4.257 [0.540]</td><td>1.287 [0.142]</td><td>3.31</td></tr>
<tr><td>MelJuSo</td><td>4.397 [0.563]</td><td>1.075 [0.165]</td><td>4.09</td></tr>
<tr><td>MiaPaCa2</td><td>1.937 [0.557]</td><td>0.601 [0.295]</td><td>3.22</td></tr>
<tr><td>BxPC3</td><td>4.859 [3.276]</td><td>1.334 [0.737]</td><td>3.64</td></tr>
<tr><td>Panc-1</td><td>2.887 [0.592]</td><td>0.636 [0.240]</td><td>4.54</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Study</th><th>Setup</th><th>Objectives and results</th></tr>
<tr><td>Selumetinib

N-desmethyl selumetinib

Inhibition of tumour cell viability

Pharmacology Report 06

(non GLP) 2012</td><td>A panel of tumour cell lines. Viable cell number was determined using the MTS proliferation assay</td><td><u>Objective</u>: compare the ability of AZD6244 and the N-desmethyl metabolite of AZD6244 to inhibit cell viability of a panel of three different tumor cell lines

<u>Results</u>: N-desmethyl metabolite of AZD6244 is at least 5-fold more active than AZD6244
<table>
<tr><th>Compound</th><th>Cell line</th><th>Expt 1^</th><th>Expt 2^</th><th>Expt 3^</th><th>Geomean</th><th>S.E.</th><th>Ratio*</th></tr>
<tr><td>AZD6244</td><td>A375</td><td>0.018</td><td>0.0165</td><td>0.0208</td><td>0.01835</td><td>0.0013</td><td>5.39</td></tr>
<tr><td></td><td>A2058</td><td>0.754</td><td>0.621</td><td>0.38</td><td>0.5629</td><td>0.1091</td><td>7.04</td></tr>
<tr><td></td><td>MelJuSo</td><td>1.11</td><td>1.98</td><td>1.23</td><td>1.3930</td><td>0.2722</td><td>5.67</td></tr>
<tr><td>N-Desmethyl</td><td>A375</td><td>0.0034</td><td>0.0024</td><td>0.00485</td><td>0.0034</td><td>0.0007</td><td></td></tr>
<tr><td>metabolite</td><td>A2058</td><td>0.139</td><td>0.0517</td><td>0.07</td><td>0.0799</td><td>0.0265</td><td></td></tr>
<tr><td></td><td>MelJuSo</td><td>0.102</td><td>0.47</td><td>0.31</td><td>0.2459</td><td>0.1065</td><td></td></tr>
</table>
* AZD6244:N-desmethyl AZD6244 Geomean ratio
^ raw data from E Book E11508</td></tr>
<tr><td>Selumetinib

N-desmethyl selumetinib

Inhibition of phorbol ester stimulated Erk phosphorylation in whole blood

Pharmacology Report 07 (non GLP) 2012</td><td>Human whole blood derived leucocytes
ERK phosphorylation measured by flow cytometry assay</td><td><u>Objective</u>: to compare the inhibition of phorbol ester stimulated phosho-ERK production in human whole blood by AZD6244 and its metabolite, N-desmethyl AZD6244

<u>Results</u>: N-desmethyl AZD6244 showed increased potency compared to AZD6244
<table>
<tr><th>Compound</th><th>IC_{50} (nM) ± S.E.</th></tr>
<tr><td>AZD6244</td><td>460 ± 137</td></tr>
<tr><td>N-desmethyl AZD6244</td><td>266 ± 168</td></tr>
</table></td></tr>
<tr><td>Selumetinib

Amide selumetinib

Inhibition of Erk phosphorylation in tumour cell lines

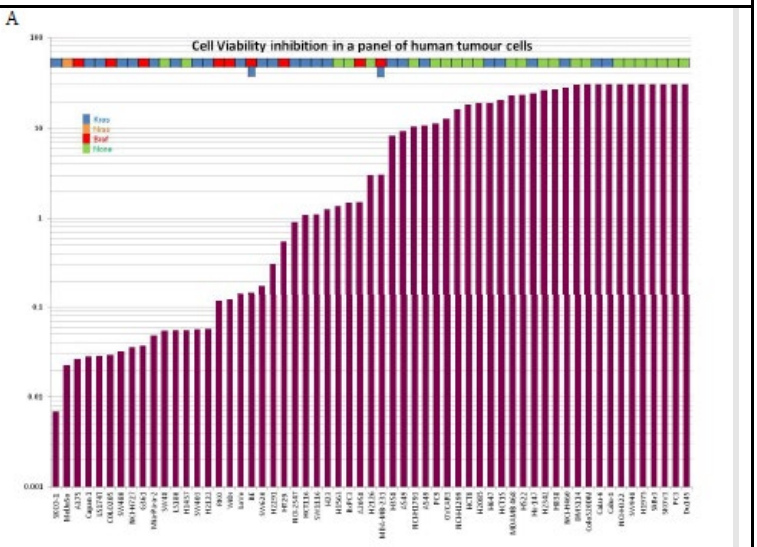
Pharmacology Report 08 (non GLP) 2012</td><td>A panel of tumour cell lines, ERK phosphorylation measured by a PACE assay (Probe Assay—Chemiluminescence Enhanced)</td><td><u>Objective</u>: compare the ability of AZD6244 and its amide metabolite to inhibit the phosphorylation of ERK in three different tumour cell lines

<u>Results</u>: amide metabolite is up to 50 fold less active than parent AZD6244 for inhibition of phosphorylation of ERK
<table>
<tr><th>Cell line</th><th>AZD6244
IC_{50} nM [SE]</th><th>AZD6244 amide metabolite
IC_{50} nM [SE]</th><th>Ratio</th></tr>
<tr><td>A375</td><td>23.69 [2.73]</td><td>913.9 [43.2]</td><td>39</td></tr>
<tr><td>A2058</td><td>20.15 [1.21]</td><td>784.88 [49.67]</td><td>39</td></tr>
<tr><td>Calu-6</td><td>15.04 [0.16]</td><td>759.21 [38.53]</td><td>50</td></tr>
</table>
Each experiment was performed 4 times. SE = standard error.</td></tr>
<tr><td>Selumetinib

Inhibition of cell viability in BRAF and KRAS mutant tumour cell lines by AZD6244

Pharmacology Report 35 (non GLP) 2019</td><td>Recombinant MEK1/2 enzyme FRET-Based Z'Lyte Kinase Activity Assays</td><td><u>Objective</u>: determine the effects of AZD6244 on cell viability of a variety of human tumour cell lines in which the mutation status BRAF and KRAS is known in vitro

<u>Results:</u> The majority of the cell lines classed as sensitive (IC_{50} <1 µM) carry either a BRAF or KRAS gene mutation</td></tr>
</table>

<table>
<tr><th>Study</th><th>Setup</th><th>Objectives and results</th></tr>
<tr><td></td><td></td><td>A
 

X axis = cell line name
Y axis = cell viability inhibition IC_{50} in µM</td></tr>
<tr><td>Selumetinib

Inhibition of MEK1/2 enzyme

Pharmacology Report 45 (non GLP) 2016</td><td>Recombinant MEK1/2 enzyme FRET-Based Z'Lyte Kinase Activity Assays</td><td><u>Objective</u>: determine the activity of AZD6244 on the MAP2K1-MAPK1 and MAP2K2-MAPK1 pathways.

<u>Results:</u>
<table><tr><th>Kinase Names</th><th>[ATP] µM</th><th>IC_{50} (nM)</th></tr><tr><td>MAP2K1 (MEK1)</td><td>100</td><td>222</td></tr><tr><td>MAP2K2 (MEK2)</td><td>100</td><td>389</td></tr></table></td></tr>
<tr><td>Selumetinib

Inhibition of MEK1/2 enzyme

Pharmacology Report 46 (non GLP) 2016</td><td>Recombinant MEK1/2 enzyme radiometric kinase assays</td><td><u>Objective:</u> determine the activity of AZD6244 on the enzymatic activity of MEK1 and MEK2.

<u>Results:</u>
<table><tr><th>Kinase</th><th>[ATP] µM</th><th>IC_{50} µM 1</th><th>IC_{50} µM 2</th><th>IC_{50} µM 3</th><th>Mean pIC_{50}</th><th>Geomean IC_{50} µM</th></tr><tr><td>MEK1</td><td>10</td><td>0.382</td><td>0.417</td><td>0.453</td><td>6.38</td><td>0.416</td></tr><tr><td>MEK2</td><td>10</td><td>0.405</td><td>0.434</td><td>0.366</td><td>6.40</td><td>0.401</td></tr></table></td></tr>
<tr><td>Selumetinib

N-desmetyl selumetinib

Amide selumetinib

Inhibition of MEK1 enzyme

ATP competition assessment

Pharmacology Report 56 (non GLP) 2019</td><td>Human recombinant MEK1 enzyme [γ-33P] ATP - Based Radiometric Assay</td><td><u>Objective:</u> determine the activity of AZD6244 and its two metabolites on MAP2K1 and to understand if AZD6244 shows competitive inhibition with ATP

<u>Results:</u>
AZD6244 caused inhibition of MAP2K1 IC_{50} = 15.3 nM, not competitive with respect to ATP.
N-desmethyl metabolite approx. 2-fold more potent than AZD6244
amide metabolite is approx. 18-fold less potent than AZD6244
<table><tr><th>Kinase Name</th><th>IC_{50}</th><th>ATP concentration (µM)</th></tr><tr><td>MAP2K1 (human)</td><td>AZD6244
15.3 nM (stdev 0.9 nM)</td><td>10</td></tr><tr><td>MAP2K1 (human)</td><td>N-desmethyl metabolite of AZD6244
6.7 nM (stdev 1.3 nM)</td><td>10</td></tr><tr><td>MAP2K1 (human)</td><td>Amide metabolite of AZD6244
272 nM (stdev 88 nM)</td><td>10</td></tr></table><table><tr><th>Kinase Name</th><th>Km</th></tr><tr><td>MAP2K1 (human)</td><td>2.2 µM (stdev 0.6 µM)</td></tr></table></td></tr>
</table>

Selumetinb and its metabolites have not been tested against MEK of other species used in toxicity studies such as mouse, rat, rabbit and Cynomolgus monkey.

Assays in several tumour cell lines have been used to demonstrate selectivity for RAF-MEK-ERK pathway inhibition over other related signalling pathways. Tumour cell lines whose growth was most potently inhibited by selumetinib were enriched for those carrying RAS and BRAF gene mutations and which therefore have active RAF-MEK-ERK signalling (Davies et al, 2007; Dry et al, 2010). None of the tumour cell lines was derived from neurofibrosarcoma, Schwann cells or of nervous system origin.

Primary pharmacodynamics *in vivo*

Selumetinib was originally developed for treatment of several cancers and later in treatment of paediatric patients NF1 and PN.

Selumetinib was initially assessed in anti-tumour efficacy using human tumour xenografts (oncology proof of concept models (POC). Three studies were performed using the Calu-6, mutant KRAS non-small-cell lung carcinoma human tumour xenograft grown subcutaneously in mice. Selumetinib was administrated orally and a dose response study was observed. The minimal effective dose was determined at 0.75 mg/kg BID and a statistically significant inhibition of tumour growth was observed. Moreover, at doses generating clinically relevant exposures, the maximal inhibition of ERK phosphorylation was between 40% and 80% (Pharmacology Reports 09, 10, 12 and 47).

To investigate anti-tumour efficacy in the intended indication, genetically modified mouse models of neurofibroma type-1 (deletion of NF1 in Schwann cell precursors results in neurofibroma formation) were used in two studies. Selumetinib resulted in inhibition of ERK phosphorylation (40 - 60%) and in reduction in number (up to 75%) and size (up to 41%) of neurofibromas at dose which were close to clinically relevant dose (in term of human equivalent dose [HED]) (Pharmacology Reports 54 and 55).

Secondary pharmacodynamic studies

Selumetinib and N-desmethyl selumetinib were tested at 10 µM (390-fold greater than the unbound plasma Cmax of selumetinib and > 3000-fold greater than the unbound plasma C_{max} of N-desmethyl selumetinib at the recommended selumetinib clinical dose of 25 mg/m² BID) in a panel of *in vitro* radioligand binding and enzyme assays covering a diverse range of molecular targets. No targets were identified that were considered pharmacologically relevant at human therapeutic plasma exposure levels of selumetinib (unbound C_{max} = 26 nM) or N-desmethyl selumetinib (unbound C_{max} = 3 nM) (Study 0320SY).

Safety pharmacology programme

Selumetinib was evaluated in a series of GLP-compliant safety pharmacology studies in *vitro* and *in vivo*. No safety concerns have been identified in the safety pharmacology studies conducted with selumetinib and its main metabolite N-desmethyl selumetinib at clinically relevant doses.

The CNS/neurobehavioral safety profile was assessed in rats. In an Irwin assay in male rats, selumetinib (10, 30, 100 mg/kg, oral route, single dose) did not induce any adverse neurobehavioral effects at the oral doses up to 100 mg/kg (study 1758/ARR/03). However, no PK measurement have been performed.

The respiratory effects of selumetinib were investigated in the anaesthetised rat (Study 1760/ARR/03). After single oral gavage administration of selumetinib (10, 30, 100 mg/kg, oral route) in male rats, there was no effect on respiratory rate, tidal volume, lung dynamic compliance or minute volume up 100 mg/kg. Airway resistance was slightly increased (18% above baseline) at 2 hours post-dose in the 100 mg/kg dose group only. There were no respiratory abnormalities observed in the rat 29-day

toxicity study at this dose level. No PK measurement have been performed. Concentration and exposure at 100 mg/kg in rat are respectively around 36-fold the clinical intended Cmax and 42-fold intended exposure at the recommended clinical paediatric dose (25 mg/m² bid) considering TK measurements at D1 in 29-day toxicity in rat (223-002).

Two safety pharmacology studies addressed the potential adverse cardiovascular or cardiac electrophysiological effects of selumetinib (studies 030819.BCP and 0179SZ). In the hERG assay, selumetinib was evaluated in stably transfected HEK293 cells at concentrations of 0.1, 0.3, 1 and 3 and 10 µM, which produced no concentration-dependent inhibition of hERG tail current. This maximum test concentration was 390-fold greater than the unbound plasma Cmax of selumetinib the recommended selumetinib clinical dose of 25 mg/m² BID. *In vivo* safety pharmacology (telemetry) studies were performed in conscious minipigs (study 1759/ARR/03). Oral dosing of selumetinib (0, 3, 10 and 30 mg/kg) had no effects on heart rate, blood pressure or ECG intervals (QT, QTc, RR, PR) neither up to 30 mg/kg (below the clinical Cmax at 25 mg/m² BID). Likewise, selumetinib had no effect on electrocardiographic parameters in monkey after 26-week administration up to 4 mg/kg BID (approximately 4-fold the expected clinical Cmax at the recommended dose). N-desmethyl selumetinib did not inhibit the hERG current at concentrations up to 100 µM (>30000-fold the clinical unbound Cmax at 25 mg/m² BID). The presence of N-desmethyl selumetinib in minipig CV study was not investigated.

Regarding GI system, in the rat studies, treatment with a single dose of selumetinib was associated with observations of gastric irritation at 30 and 100 mg/kg (approximately 24- and 42-fold respectively the clinical exposure at 25 mg/m² BID). GI findings were observed in rat and monkey toxicity studies; however, no histopathological evidence of gastric irritation was observed. Erosion/ulceration in the non-glandular mucosa of the stomach has been observed in mice at from 1 mg/kg, the lowest dose tested in 26-week study, therefore no safety margin could be determined (studies 1761/ARR/03, 1762/ARR/03 and 1763/ARR/03).

Pharmacodynamic drug interactions

No non-clinical pharmacodynamics drug interaction studies were conducted.

2.3.3. Pharmacokinetics

Methods of analysis

The multi-analyte analytical methods used to assay selumetinib and both its N-desmethyl and amide metabolites in non-clinical pharmacokinetic and pivotal toxicology studies employed LC-MS/MS. Toxicokinetic bioanalysis was conducted with validated assays. Samples of selumetinib, selumetinib N-desmethyl, and selumetinib amide in mouse, rat and monkey plasma were shown to be stable for the required storage period and during analysis. All bioanalysis met validation and qualification criteria applicable at the time of the study.

Stability of selumetinib and N-desmethyl selumetinib in plasma samples of mouse, rat and monkey stored at ca. -20°C were demonstrated over a 4-months storage period and that of selumetinib amide over a 12-month storage period.

Absorption

In vivo the absorption of selumetinib was studied in mice, rats and monkeys after oral and IV single dose administration and after repeated doses (PK dedicated studies or PK parameters measured in toxicity studies – Studies KPM017, KPR024, KKP023, VKS/0211, 0428PM KMM058, VKS0210 and 0070DP). Two forms were studied: earlier studies were performed with selumetinib free base showing

a moderate to high absorption at low doses in all species but at higher doses evidence of saturable absorption was observed. On the contrary, observed exposure after selumetinib hyd-sulfate salt administration increased approximately proportionally with the dose. The second form was therefore selected for the further non-clinical and clinical development.

After oral administration selumetinib hyd-sulfate was rapidly absorbed in all species studied with Tmax occurring after 1-2 h in mice and monkeys and after 2-4 h in rats. The clearance was measured only in monkeys with selumetinib free base and the value indicated that clearance was moderate (0.88 L/h/kg) and volume of distribution greater than total body blood volume (1.1 L/kg). The bioavailability of selumetinib after oral intake was also determined only in monkey at 56 %. The half-time T½ was determined at 3-7.6h in mice, 2.95-11 h in monkeys after PO intake of selumetinib hyd-sulfate and these values were similar to the half-life observed in humans (6.2 h in paediatric patients after the intended recommended dose). No accumulation was observed in mice after repeated dose administration and low accumulation occurred in monkeys (max 1.9). Sex-differences were observed in mice; exposures were 2-fold higher in females while no sex-differences were observed in monkeys.

PK parameters of N-desmethyl selumetinib were also measured after selumetinib hyd-sulfate salt administration. This active metabolite was formed with Tmax occurring at 0.6-10 h and was present in mice around 2-20% in 26-weeks study and up to 30% in carcinogenicity study, with lower proportion relative to selumetinib with time period, while it was present at very limited quantity in rats and in monkeys (< 0.2% at 3 months in rats and 1-month in monkeys and not detected in 26-weeks). In mice, N-desmethyl selumetinib presented a T1/2 similar than the parent (2.9-7h), a lower bioavailability, a higher clearance and volume of distribution. No accumulation was observed. Exposure to N-desmethyl selumetinib was higher in male mice than in females. The half-life T½ was determined at 3-8h in mice and 5-7 h in monkeys.

PK parameters of selumetinib amide were also measured after selumetinib hyd-sulfate salt administration. This second active metabolite was rapidly formed with Tmax occurring at 0.5-24 h and was present in around 2% in mice, monkeys and rats. Exposures were increased with multiple dosing. The half-life T½ was determined at 4-27 h in mice.

Distribution

The *in vitro* plasma protein binding of selumetinib and N-desmethyl selumetinib have been studied in mouse, rat, dog, mini-pig, monkey and human (studies KPJ003 and KPJ027). In all species selumetinib showed similar high protein binding profile. The determined plasma protein binding was found to be independent of concentration for both compounds. Binding of selumetinib was high in all species investigated and very high in rat, with overall mean binding ranked minipig (93.7%) < dog (94.6%) < monkey (97.7) < human (98.4%) < mouse (98.9%) < rat (99.7%). Binding was determined for its metabolite: binding was also high in all species investigated and very high in rat.

The tissue distribution of total radioactivity in albino male rats and male and female pigmented rats and mice following single oral administration of [^{14}C]selumetinib was evaluated by quantitative whole-body autoradiography (QWBA) (studies KMR002 and KMM004). Total radioactivity was widely distributed with tissue concentrations generally lower than blood and minimal penetration into the CNS and was then eliminated rapidly from the tissues. High concentrations were found in the stomach, intestine, lung, liver, kidney and adrenal gland, but there was no evidence of high affinity melanin-specific binding of radioactivity in the pigmented tissues (pigmented skin and uveal tract). Levels of radioactivity in the whole eye was persistent and the T1/2 was determined by liquid scintillation counting (LSC) at 60 h.

The tissue distribution of total radioactivity was also determined in female nude mice bearing subcutaneous Calu-6 xenografts after a single oral administration of [14C]-selumetinib. Systemic distribution of radioactivity was similar in rat. Tumour concentrations were lower than blood levels up to 12 hours post dose, however the radioactive concentration remained measurable in the tumour for longer than most other tissues.

Metabolism

The *in vitro* metabolism of selumetinib was evaluated in liver microsomes and hepatocytes of mouse, rat, dog, monkey and human and *in vivo* in mice, rat, dog, monkey and human, respectively (studies KMN011, BE000898-44, BE000726-85, KMX028, KMN012).

In vitro experiments indicated Phase 1 metabolic reactions including oxidation of the side chain, N-demethylation, and loss of the side chain to form amide and acid metabolites. The N-desmethyl metabolite was formed in hepatocyte incubations in human and mouse but not in rat and monkey. The majority of metabolites were detected as glucuronide conjugates *in vitro*, indicating that Phase 2 conjugation is likely to be a significant route of elimination for selumetinib. The major circulating metabolite M2 (selumetinib amide glucuronide[-2H]) in the human ADME study (YAU169) was observed following incubation of selumetinib with rat and human hepatocytes, and in rat and mouse plasma. In study KMN012, CYP3A4 was the predominant CYP isoform responsible for selumetinib oxidative metabolism with CYP1A2, CYP2C9, CYP2C19, CYP2E1 and CYP3A5 also involved to a lesser extent. This was supported by evidence that CYP3A4 is the principal isoform in formation of the imidazoindazole metabolite M10 which is intermediate in the formation of the major glucuronide metabolite M2 found in human plasma and urine (studies ADME-AZS-Wave3-150302, ADME-AZS-Wave3-150422, 110331_CRP_kmnm633, BE000021-21, BS001696-61 and KMN045). Formation of the active N-desmethyl metabolite appeared primarily mediated by CYP2C19 with *in vitro* evidence for contributions from CYP1A2, CYP2A6, CYP2C9 and CYP2C8. N-desmethyl metabolite is subsequently metabolised through a similar pathway to selumetinib.

The principal enzymes responsible for the *in vitro* metabolism of [14C]-selumetinib by direct glucuronidation were investigated by incubation with nine recombinant UGT enzymes. Formation of a single metabolite was extensive. After a 60-minute incubation with UGT1A1 and UGT1A3 this metabolite accounted for approximately 51.5 and 23.0% of chromatogram radioactivity, respectively. No other UGT enzymes produced any peaks that were not present in the corresponding controls.

The dog has not been used in safety pharmacology and toxicity studies. Only limited "historical" *in vivo* data are available for this species. Selumetinib was shown to be metabolised by N-demethylation, loss of the side chain to form the acid (M15) and amide (M14) metabolites, and direct conjugation with glucuronic acid (M4 or M7) as well as desfluorhydroxy selumetinib amide. Peak concentrations of N-desmethyl selumetinib (M8) were less than 3% of those of selumetinib in dog plasma. The plasma samples for metabolite identification were derived from study 0391KD.

The cynomolgus monkey has been used as the non-rodent species in repeat-dose toxicity studies. The studies to investigate the metabolite profile *in vivo* in monkeys and the toxicokinetic investigations showed that the metabolism of selumetinib to N-desmethyl selumetinib was very low or absent. Selumetinib amide was not identified in the metabolism studies in monkeys but was detected in plasma samples of monkeys obtained from the 26-week repeat dose toxicity study at levels based on the $AUC_{(0\text{-}12)}$ on average 2.3% and 36.1% of those of selumetinib on Day 1 (Week 1) and Week 26, respectively. The major human metabolite M2 (selumetinib amide-glucuronide -2 atomic mass units) has not been definitely identified *in vivo* in monkey metabolism studies.

An additional in vitro study (BE002560-24) has been conducted by the applicant to assess the formation of M2, desfluorohydroxy selumetinib amide glucuronide and the N-desmethyl metabolite

following incubation of selumetinib in mouse, rat, dog, monkey and human hepatocytes. The results of this study demonstrated the presence of M2 and the absence of the desfluorohydroxy AZD6244 amide glucuronide in all the other species including monkey. The active metabolite M8 (N-desmethyl selumetinib) was detected in mouse, dog and human hepatocytes, but not in monkey or rat hepatocytes, a finding consistent with the earlier *in vitro* cross-species study (KMN011).

Excretion

Excretion balance has been performed in intact and bile duct cannulated rats, monkey and mouse. The studies indicated that fecal elimination was the dominant route, whereas urinary excretion was minor. Biliary elimination was shown to play a major role in bile duct cannulated rats. Excretion was rapid in rodent (within 48h) but longer in monkeys (up to 120h).

2.3.4. Toxicology

The oral route of administration was used in all toxicology studies to match the intended clinical administration route, twice daily dosing in monkey, mouse and human; once daily dosing in rat.

Single dose toxicity

There were no adverse effects of selumetinib following single oral doses to SD rats (up to 300 mg/kg). In monkeys, transient changes in clinical pathology parameters (liver, lymphoid system) were observed and the NOEL was established at 30 mg/kg twice daily (studies 223-001 and 1638-213).

Repeat dose toxicity

Selumetinib free base

Selumetinib free base was firstly developed and studied in toxicity studies in SD rat and cynomolgus monkey. In this early development, two studies were performed in rat (14-day and 28-days) and one in monkeys (28-day) with selumetinib free base.

In rat, selumetinib was administrated by oral gavage once a day (unlike the treatment in other species: mouse and monkey). The 14-day study demonstrated that the MTD was above 300 mg/kg/day (the highest dose tested); however, no Toxicokinetic (TK) analysis was performed to determine the selumetinib free base level. In 29-day study, GI tract was identified as the main target organ and mineralisation of the gastric mucosa was observed in all dose in males and ≥ 30 mg/kg/day in female; therefore no NOAEL was determined in males and the lowest dose 10 mg/kg/day was determined in females as the NOAEL. In 29-day study in monkeys, selumetinib demonstrated a reversible GI intolerability but no NOAEL was therefore determined. The later development was performed with selumetinb hyd-sulfate which is the form used in human.

Selumetinib hyd-sulfate

In all pivotal repeat-dose toxicity studies, animals were administrated selumetinib hyd-sulfate. The main target organs of toxicity in the repeat dose studies were skin, bone, GI tract, lower urinary tract and cornea. Soft tissue mineralisation was noted in gastric mucosa, cornea, kidney, liver, myocardium, skeletal muscle and stomach in rodents.

Mortality

Selumetinib-related mortalities occurred in mice, rats and monkeys.

In mice 7-day (>242 mg/kg BID), 1-month (≥103 mg/kg BID) and 26-week (20 mg/kg BID) repeat dose studies in CD-1 mice (studies 0354DM, 0355DM and VKS/0211), administration of selumetinib

hyd-sulfate was not tolerated and resulted in mortality. Selumetinib-related mortality also occurred at 100 mg/kg BID in CByB6F1 hybrid female mice in dose range finding (DRF) for carcinogenicity assessment. The main cause of death in these animals was most likely due to microscopic changes in the gastrointestinal tract. The mean exposure at which these deaths occurred were at least 28-fold the free AUC in humans at the MRHD of 25 mg/m² BID. In the 26-week study in mice, dosing of selumetinib hyd-sulfate at 20 mg/kg BID (similar exposure, around 28 x the free AUC in humans at the MRHD) resulted in vascular engorgement of the corpus cavernosum of the bulbocavernosus muscle in male mice, which in some animals resulted in obstruction of the urinary tract leading to premature deaths between Week 8 and 15. The mechanism underlying these changes is unknown. Premature deaths in this group also occurred between Weeks 11 to 25. These early deaths were also accompanied by a result of marked inflammatory changes in the large intestine, in particular the colon and caecum, with occasional perforation and occasional extension to the serosa.

In the 3-month rat study (study 528088), administration of selumetinib hyd-sulfate at 20 mg/kg/day in males and 25 or 50 mg/kg/day in females was not tolerated. All animals in these dose groups were euthanized (Days 26 or 30). The clinical signs responsible for death or euthanasia animals included multiple skin lesions and/or scabs in the dorsal and abdominal regions, excessive grooming/scratching, fur erected/ungroomed and ploughing. These deaths occurred at least 91-fold the total AUC in humans at the maximum clinical dose of 25 mg/m² BID.

In the 29-day monkey study (1639-213), severe GI intolerance (persistent diarrhoea and/or dehydration) were observed after selumetinib free base administration at 3, 10 and 30 mg/kg BID (similar exposure to that observed at the clinical total AUC). High volume of Captisol seems to enhance GI toxicity observed with selumetinib. In an MTD study in monkeys (VKS/0153) with selumetinib hyd-sulfate at escalating doses, one male was euthanized at 15 mg/kg bid after 10 days administration of this dose with GI intolerance.

Skin

In rat studies, dose-dependent skin lesions/scabs were observed in females at doses ≥ 25 mg/kg/day (160x the total clinical AUC) for 14 days, in females at ≥ 2.5 mg/kg/d (21x the total clinical AUC) and males at ≥ 5 mg/kg/d (32 x the total clinical AUC) for 3 months and these skin effects were correlated with microscopic ulceration at high doses. In 3-month study, NOAEL could be established only in males at 2.5 mg/kg/day, the calculated safety margin was 15 times the clinical total AUC. In the longest study (2-year carcinogenicity study) dose dependent microscopic findings of erosions/ulcers in skin were observed in males at ≥ 0.8 mg/kg/day (5.5x the clinical total AUC or equivalent to the clinical exposure for free AUC) and ≥ 1 mg/kg/day in females (15x the clinical total AUC or 2.9x the clinical free AUC), NOAEL could be established in males at 0.25 mg/kg/d and in females at 0.3 mg/kg/d, the calculated safety margin was 3 in female and there was no safety margin in male.

Gastrointestinal tract

In mice, GI tract findings were observed after selumetinib administration at ≥ 11 mg/kg BID (19.5x the clinical free AUC) in 1-month study and ≥ 1 mg/kg BID (2x the clinical AUC) in 26-week study. No NOAEL could be determined and no safety margins could be calculated. These GI effects were characterised by focal ulceration, inflammation and/or mucosal hypertrophy in the caecum, focal colonic serositis, focal degeneration in duodenal Brunner's glands; glandular epithelial cell degeneration and acute inflammatory cell infiltration in stomach, glandular mucosal erosion/ulceration and inflammation and sub-mucosal and serosal inflammation. Similar selumetinib-related changes in the GI tract were seen in the 1-month DRF study in males and in females CByB6F1 hybrid mouse at higher exposure.

In monkey, administration of selumetinib hyd-sulfate to monkeys for up to 26 weeks was also associated with GI finding and dose-limiting finding. Loose/liquid feces were observed at 1.5 mg/kg BID in females (similar to the clinical AUC) and at 4 mg/kg BID in males (7x the clinical free AUC). No corresponding histopathological changes in the GI tract were observed. Diarrhoea was associated with signs of dehydration and/or body weight loss requiring a brief dosing holiday or hydration intervention. There was evidence of recovery from the GI effects and the associated clinical pathology changes following a dosing holiday.

Bone

In 3-month rat study, microscopic findings were observed in the femoro-tibial joint at a total exposure at least 11-fold greater than the clinical free exposure at 25 mg/m² BID. In males dosed with 10 mg/kg BID selumetinib, physis dysplasia was observed in the femur and, in females at 12.5 mg/kg BID, there was decreased cellularity in the bone marrow of the femur adjacent to the physis. Safety margins for these effects were calculated at 6.1 in males and 11.5 in females (free AUC). Physeal dysplasia was not observed in the 2-year rat carcinogenicity study at exposures around 2.9- and 3.7-fold greater than the clinical free AUC at 25 mg/m² BID in males and in females, respectively.

Soft mineralisation

Dose dependent soft tissue mineralisation (calcium) was observed in a variety of tissues in rats and mice.

In mice, various tissues including gastric mucosa, cornea, kidney, liver, myocardium, skeletal muscle and stomach were observed at dose levels ≥ 11 mg/kg BID (19.5x the clinical free AUC) in the 1-month study. Mineralisation was associated with changes in plasma inorganic phosphate, calcium and albumin in both species. Whilst similar biochemistry changes were observed in the 26-week study, tissue mineralisation was restricted to minimal multifocal mineralisation in the liver, in only a small number of animals at 20 mg/kg BID (28x the mean clinical free AUC). These findings were persistent after one-month recovery period in other tissues and after 13-weeks recovery in liver. No NOAEL could have been determined in mice for this toxic effect and no safety margins could have been calculated. Tissue mineralisation with selumetinib has not been observed in monkey.

In rats, soft tissue mineralisation was also noted in a number of organs stomach, kidney, aorta, heart, mesenteric lymph node, lung and tongue at doses ≥ 1mg/kg/day in males (7x clinical total AUC or 1.3x clinical free AUC) and ≥ 2.5 mg/kg/day in females (21x clinical total AUC, or 4x clinical free AUC). Reversibility was not assessed in this study.

Urinary lower tract

Vascular engorgement of the corpus cavernosum of the bulbocavernosus muscle were observed in 26-week mice at a dose of 20 mg/kg BID (28 times the free AUC in humans at the MRHD leading to significant urinary tract obstruction as well as inflammation and luminal haemorrhage of the urethra leading to early death in male mice.

Cornea

In 1-month study in mice, ophthalmology findings (oval opacities across the cornea, rough appearance to the surface of the cornea) were observed at all doses and histopathologic exam revealed a dose-dependent mineralisation of the cornea which is not reversible after cessation of treatment. No NOAEL was established and no safety margin could be determined. Moreover, in 26-week carcinogenicity study, eye was also a target organ since higher incidence of adenoma in Hardarian gland were observed at mid-dose. Ocular malformations were also observed in reproductive toxicity studies. Finally, in correlation to these toxic effects, tissue distribution study demonstrated that selumetinib was persistent in the whole eye (T1/2 around 60h).

Genotoxicity

A complete package of genotoxicity studies in agreement with the ICH S2 (R1) guideline, including tests for gene mutations in bacteria and chromosomal aberrations *in vitro* and *in vivo*, was performed to assess the genotoxic potential of selumetinib.

Selumetinib free base did not induce mutations when adequately tested in five histidine-requiring strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537 and E.coli WP2 uvrA) at concentrations up to 5000 µg/plate in the absence and in the presence of a rat liver metabolic activation system (S9). In the *in vitro* mammalian chromosome aberration test in mouse lymphoma cells, selumetinib free base was negative at dose levels up to 150 µg/mL. In the two *in vivo* chromosomal aberration test (micronucleus), selumetinib free base induced micronuclei in the bone marrow of ICR mice (2000 mg/kg single dose at 24h collection time) and CD-1 mice (at 1000 and 2000 mg/kg at 24h collection time, equivocal response at 500 mg/kg). A NOAEL was determined at 160 mg/kg (Cmax = 68.2 µmol/L).

Centromeric staining was performed with slides form the study performed with selumetinib free base in mice. Approximately 60% of the micronuclei were centromere positive at the two clearly positive doses (1000 and 2000 mg/kg) suggestive of a threshold aneugenic mode of action. In the 26-week repeated dose study in CD1-mice, the highest tested dose (20 mg/kg BID) resulted in male at Cmax = 29.6 µg/ml, around 40-fold the Cmax at the intended recommended dose in paediatric patients (Cmax= 731 ng/ml at 25 mg/m² BID). Comparison in term of exposure (total AUC) resulted in the same ratio. The Cmax observed at NOAEL (160 mg/kg) after selumetinib free base (Cmax = 68.2 µmol/L = 31 µg/ml) was similar.

A third *in vitro* micronucleus assay was performed in CD1-mice with selumetinib hyd-sulfate to ensure higher bioavailability. Selumetinib induced micronuclei in the bone marrow from 121 mg/kg and above (2 doses 24h apart). A NOAEL was determined at 24 mg/kg; however, no TK analysis was performed. Bridging exposure at the dose of 23 mg/kg (11 mg/kg BID) from the 1-month toxicology study in the same mouse strain performed with selumetinib hyd-sulfate (0355AM) yielded a mean total AUC of 56950 ng*h/mL and a mean free AUC of 627 ng*h/mL, which resulted in safety margins to the respective human AUCs at the MRHD of 28.3-fold and 19.5-fold.

Carcinogenicity

Selumetinib was administered to male and female Wistar rats (2-year study) daily at 0.25, 0.8, or 2.5 mg/kg/d in males and 0.1, 0.3, or 1 mg/kg/d in females by oral gavage *(study 501094)*. Selumetinib was not associated with any neoplastic or pre-neoplastic findings at any dose level (up to x 2.9-3.7 fold the clinical free AUC, females and males respectively). Selumetinib-related non-neoplastic alterations that were considered to be adverse were sporadic incidences of skin erosions/ulcers which were present at higher incidence and severity in males at ≥ 0.8 mg/kg/day and at higher severity in females at 1 mg/kg/day. There was also a higher incidence of erythrophagocytosis/erythrocytosis in the mesenteric lymph node of males at 2.5 mg/kg/day. These findings were consistent with histologic findings reported in the previous studies in rat.

Selumetinib was administered to male and female Tg.rasH2 mice by oral gavage at 3, 8, or 25/15 mg/kg twice daily (6, 16, 50/30 mg/kg/day) for 6 months *(study 20086561)*. The maximum dose was 25 mg/kg BID based on DRF studies but this dose was reduced to 15 mg/kg BID from week 19 to week 26 due to unexpected toxicity consisting of mortality and body weight losses (undetermined cause of death). There were no changes in the negative group and there were expected changes in the positive control group. No increase in the incidence of any type of tumours in the selumetinib groups except an higher incidence of adenoma in Hardarian gland in 2 males at mid-dose (8 mg/kg BID, 2/25M, 8%) but this

higher incidence was still within the historical control values (0-16%, data not provided). Therefore, selumetinib was not carcinogenic in CByB6F1/Tg rasH2 hemizygous mice (up to x 16 – 24.3-fold the clinical free AUC, males and females respectively). Selumetinib-related non-neoplastic alterations that were considered to be adverse were observed in the cecum (crypt hyperplasia in males and females administered ≥ 8 mg/kg BID), colon (crypt hyperplasia in males administered ≥ 3 mg/kg BID and females administered 25/15 mg/kg BID and diverticulum in males and females administered 25/15 mg/kg BID), and spleen (increased pigmented macrophages females administered ≥ 3 mg/kg BD).

Reproduction Toxicity

A full set of developmental and reproductive studies were conducted in mice, with potential effects on male fertility evaluated in the 26-week chronic toxicity study.

No effect on mating performance and fertility was reported at up to 40 mg/kg/day in male mice. Sperm parameters remained unaffected at up to 10 mg/kg/day, the maximal dose evaluated for that endpoint since males of the high dose group were euthanized prematurely. The safety margin for male fertility was > 22 based on free AUC levels. In females, mating performance and fertility were not affected at doses up to 75 mg/kg/day, whereas a small reversible decrease in the number of live embryos was seen at ≥25 mg/kg/day. The NOAEL for both maternal toxicity and effects on reproductive performance was 5 mg/kg/day, corresponding to a safety margin of 3.5 based on free AUC levels.

Dose-range finding and pivotal embryo-foetal development studies showed treatment-related embryolethality, foetotoxicity (decreased foetal weights, delayed ossification), and teratogenicity at non-maternotoxic dose levels. In both studies, the occurrence of foetuses with open eye(s) was increased with all foetuses affected at 75 mg/kg/day. The incidences of other ocular findings presented as minor malformations (folded retina, variation in consistency of lens) were also increased at 75 mg/kg/day.

In the pivotal study, the occurrence of foetuses with open eye(s) was also reported in 3 litters of the low dose group (5 mg/kg/day). This was observed in foetuses derived from dams incorrectly administered a dose level of 75 mg/kg/day and clearly associated with causing this change during the window of developmental sensitivity. The incidence of cleft palate was increased at 75 mg/kg/day in the pivotal study, at ≥25 mg/kg/day in the dose-range finding study, and at ≥4 mg/kg/day in the pre- and post-natal development study. Overall, a developmental NOAEL cannot be determined for selumetinib in mice due to the occurrence of external malformations at ≥1 mg/kg/day (0.4-fold below the clinical free Cmax) in the PPND study. In addition to the external malformations detailed above, the latter study also showed a non-reversible decrease in pup growth and a decrease in the number of pups meeting the criterion for pupil constriction on PND21 at the non-maternotoxic dose level of 15 mg/kg/day (6-fold clinical total Cmax). Toxicokinetic evaluations reported excretion into maternal milk and pup exposure to both selumetinib and N-desmethyl selumetinib on lactation day 4.

Treatment-related external malformations were reported at subclinical exposures, while there were safety margins of 3.5 to the clinical Cmax for embryolethal and foetotoxic effects. Pups exposed during gestation and lactation at 6-fold clinical exposure (total Cmax) were shown to be affected by reduced growth and decreased ability to meet the criterion for pupil constriction at weaning. There was no overall effect on male or female fertility.

Toxicokinetic data

See repeat dose toxicity and pharmacokinetics.

Local Tolerance

No local tolerance studies have been submitted.

Other toxicity studies

Studies on impurities

One identified impurity did not generate any structural alert in SAR and the response in the Ames test was weak. Further Ames testing was conducted in line with the recommendations contained in ICH S2(R1), and was negative, demonstrating the original observed effect was due to bacterial-specific nitroreductase metabolism. One identified impurity demonstrated positive results in GLP Ames test and is considered as Class 2 impurity as defined in ICH M7(R1) was identified as being mutagenic in an Ames test .

An Ames test, conducted in accordance with the current requested guideline and GLP regulation was negative (draft unaudited report).One identified impurity has been predicted positive in silico and tested negative in an Ames test according to the applicant. Based on these data it is classified as non-mutagenic (Class 5) impurity. In addition, One identified impurity gave positive in silico (Q)SAR alerts. One impurity gave alerts in both models and thus is classified as class 3 in accordance with ICH M7(R1). It is controlled in the selumetinib hyd-sulfate manufacturing process in accordance with ICH M7(R1) control option 4.

Phototoxicity

Selumetinib absorbs light in the UV range and showed enhanced cytotoxicity in the presence of UV light, in an *in vitro* 3T3 neutral red uptake phototoxicity test at 316 and 1000 µg/mL concentrations which are 3- and 10-fold above the current ICH S10 (2013) recommended maximum concentration of 100 µg/mL. The positive phototoxicity result was seen at concentrations significantly greater (> 8000x) than the free clinical Cmax achieved at the maximum intended clinical dose of 25 mg/m² BID. The concentrations for the *in vitro* phototoxicity evaluation with selumetinib were selected based on the OECD 432 (2004) evaluation criteria which was subsequently reduced from 1000 to 100 µg/mL due to a high percentage of positive results in the update of ICH S10 (2015). IC50 for selumetinib were > 100 µg/ml. Therefore, no clear phototoxic potential was observed for selumetinib at clinically relevant concentrations.

2.3.5. Ecotoxicity/environmental risk assessment

Table 3: **Summary of main study results**

Substance (INN/Invented Name): Selumetinib			
CAS-number (if available): 606143-52-6 (943332-08-9: selumetinib hydrogen sulfate)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.55	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow} Selumetinib ionisable molecule (OCDE 107)	Log Dow = 2.55 pH 5 Log Dow = 2.58 pH 7 Log Dow = 1.78 pH 9	Potentially not B
Persistence	DT50 or ready biodegradability (OECD 308)	DT50 (12°C) = 182 d (transformation product)	Potentially vPP
Toxicity	NOEC (OECD 211)	NOEC daphnia = 0.34 mg/L	not T
PBT-statement:	The compound is not considered as not PBT		

Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Default PECsw = 0.50 Refined PECsw = 0.017	µg/L			> 0.01 threshold Y
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**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 K_{biodeg} = 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 [14C] selumetinib resulted in formation of a stable (very persistent), unidentified TP and incorporation of radioactivity into sediment organic matter
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	4900	µg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	340	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	4100	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	257000	µg/L	
$PNEC_{microorganism}$ = 26 000 µg/L $PNEC_{surfacewater}$ = 34 µg/L $PEC_{surfacewater}$ = 0.017 µg/L $PNEC_{groundwater}$ = 34 µg/L $PEC_{groundwater}$ = 0.0042 µg/L $PEC_{surfacewater}/PNEC_{microorganism}$ = 6.5 x 10-7 (<0.1) : Selumetinib is unlikely to present a risk to microorganisms $PEC_{surfacewater}/PNEC_{surfacewater}$ = 5.0 x 10-4 (<1) : Selumetinib is unlikely to present a risk to organisms in surface water $PEC_{groundwater}/PNEC_{groundwater}$ = 1.2 x 10-4 (<1) : Selumetinib is unlikely to present a risk to the groundwater environment					
Phase IIb Studies					

Sediment dwelling organism	OECD 218	NOEC	133	mg/kg	*Chironomus riparius*
$PNEC_{sediment}$ = NOEC from the *Chironomus* test / 100 = 1300 µg/kg dry wieght $PEC/PNEC_{sediment}$ = 9.2 × 10-4 (<1): Selumetinib is unlikely to present a risk to sediment organisms					

Selumetinib is not expected to pose a risk to the environment when used in accordance with the SmPC.

2.3.6. Discussion on non-clinical aspects

The submitted non-clinical studies were conducted in accordance with legal requirements, available guidelines. Scientific advices on non-clinical developmental program has been received and the CHMP advice have been followed adequately.

In *in vitro* assays, selumetinib was able to inhibit the activity of purified MEK1 enzyme with IC50 values within clinically relevant concentrations. The potency in these biochemical assays was confirmed to be similar to the potency with which selumetinib inhibited RAF-MEK-ERK signalling in a panel of tumour cell lines. The sequence and structures of MEK1 and MEK2 are highly homologous across species. Selumetinib has similar activity against MEK1 and MEK2 in inhibiting the phosphorylation of inactive ERK2. The potency of the N-desmethyl and amide metabolites of selumetinib have been tested. N-desmethyl metabolite was approximately 3 to 5-fold more potent than selumetinib in inhibiting ERK phosphorylation in tumour cell lines, the amide metabolite was 18 – 50-fold less potent than selumetinib. N-desmethyl metabolite (7% to the parent) may contribute to efficacy and/or safety after administration of selumetinib to a minor extent but it is unlikely that amide metabolite (2% to the parent) contribute to efficacy and/or safety after dosing with selumetinib.

In *in vivo* studies, selumetinib was assessed in anti-tumour efficacy model using human tumour xenografts (oncologic POC) and in genetically modified mouse models of neurofibroma type-1 in two studies. In this relevant POC, selumetinib resulted in inhibition of ERK phosphorylation (40 - 60%) and in reduction in number (up to 75%) and size (up to 41%) of neurofibromas at dose close to clinically relevant dose (in term of HED, human equivalent dose).

No off-targets were identified at relevant human therapeutic plasma exposure levels of selumetinib or N-desmethyl selumetinib.

No safety concerns have been identified in the safety pharmacology studies conducted with selumetinib and its main metabolite N-desmethyl selumetinib at clinically relevant doses. Some minor findings included respiratory effects (airway resistance) but these are not considered to be of clinical relevance. Some toxic effects were observed on GI system as observed in toxicity studies.

The non-clinical absorption, distribution, metabolism and excretion studies have been conducted in the same species as used in the toxicology studies.

Selumetinib was rapidly absorbed in all species studied with Tmax occurring after 1-2h in mice and monkeys and after 2-4h in rat. The bioavailability of selumetinib after oral intake was determined only in monkey at 56 %. The half-life T½ was determined at 3-7.6h in mice, 2.95-11 h in monkeys after PO intake of selumetinib hyd-sulfate and these values are similar as half-life seen in humans (6.2 h in paediatric patients after the intended recommended dose). No accumulation was observed in mice after repeated dose administration and low accumulation occurred in monkeys (max 1.9). Sex-differences were observed in mice; exposures were 2-fold higher in females while no sex-differences were observed in monkeys. N-desmethyl active metabolite was rapidly formed in mice around 2-20% in 26-weeks study and up to 30% in carcinogenicity study (T1/2 similar than the parent, no accumulation). Selumetinib amide was rapidly formed, around 2%, in mice, monkeys and rats (T1/2 longer than the parent, no accumulation).

In all species selumetinib showed similar high protein binding profile. The *in vivo* tissue distribution in rat showed that selumetinib was widely distributed to tissues and organs and was then eliminated rapidly from the tissues. High concentrations were found in the stomach, intestine, lung, liver, kidney and adrenal gland. Levels of radioactivity in the whole eye was persistent and the T1/2 was determined by LSC at 60h.

Selumetinib was metabolised through Phase 1 metabolic reactions including oxidation of the side chain, N-demethylation, and loss of the side chain to form amide and acid metabolites. The majority of metabolites were detected as glucuronide conjugates, indicating that Phase 2 conjugation is likely to be a significant route of elimination for selumetinib. The major circulating metabolite M2 (selumetinib amide glucuronide[-2H]) in the human ADME study (YAU169) was observed following incubation of selumetinib with rat and human hepatocytes, and in rat and mouse plasma. CYP3A4 was the predominant CYP isoform responsible for selumetinib oxidative metabolism with CYP2C9, CYP2C19, CYP2E1 and CYP3A5 also involved to a lesser extent. This is supported by evidence that CYP3A4 is the principal isoform in formation of the imidazoindazole metabolite M10 which is intermediate in the formation of the major glucuronide metabolite M2 found in human plasma and urine. Formation of the active N-desmethyl metabolite appears to be primarily mediated by CYP2C19 with *in vitro* evidence for contributions from CYP1A2, CYP2A6, CYP2C9 and CYP2C8.

In nonclinical species, selumetinib was excreted predominantly faeces, whereas urinary excretion was minor, as well as in human.

In vitro pharmacokinetic drug interaction studies were reported in section 2.4.2 of this report.

The toxicological profile of selumetinib has been characterised via oral repeat-dose in rat initially and later in mice and monkeys (twice daily dosing in monkey, mouse and human; once daily dosing in rat).

In all pivotal repeat-dose toxicity studies, animals were administrated selumetinib hyd-sulfate.

The main effects in mice, rats and monkeys seen after selumetinib exposure were in the skin, GI tract and bones. Scabs associated with microscopic erosions and ulceration at a free exposure similar to the clinical exposure (free AUC) at the MRHD were seen in rats. Inflammatory and ulcerative GI tract findings associated with secondary changes in the liver and lymphoreticular system at free exposures approximately 19.5 times the clinical free AUC at the MRHD were observed in mice. Growth plate (physeal) dysplasia was seen in male rats dosed for up to 3 months with selumetinib at a free exposure 11 times the clinical free AUC at the MRHD. GI findings showed evidence of reversibility following a recovery period.

The skin effects were dose and time dependent and are relevant at clinical exposure. Reversibility for skin toxicities and physeal dysplasia was not evaluated. Vascular engorgement of the corpus cavernosum of the bulbocavernosus muscle were observed in male mice in a 26 week study at a dose of 40 mg/kg/day (28 times the free AUC in humans at the MRHD) leading to significant urinary tract obstruction as well as inflammation and luminal hemorrhage of the urethra leading to early death in male mice. The human experience showed no AE on erectile function and these effects cannot be explained by the pharmacology of selumetinib.

In 1-month study in mice, ophthalmology findings (oval opacities across the cornea, rough appearance to the surface of the cornea) were observed at all doses and histopathologic exam revealed a dose-dependent mineralisation of the cornea which is not reversible after cessation of treatment. No NOAEL and no safety margin could be determined. Moreover, in 26-week carcinogenicity study, eye was also a target organ since higher incidence of adenoma in hardarian gland were observed at mid-dose. Ocular malformations were also observed in reproductive toxicity studies. Finally, in correlation to these toxic effects, selumetinib was shown to be persistent in the whole eye (T1/2 around 60h) in tissue distribution study. An ophthalmological evaluation is recommended prior to treatment initiation and at

any time a patient reports new visual disturbances as mentioned in SmPC section 4.4 ocular toxicity subsection.

Dose dependent soft tissue mineralisation was observed after selumetinib administration in a variety of tissues in rats and mice but not in monkeys. These findings were persistent after cessation of treatment and are consistent with the primary pharmacology of selumetinib and also observed with other MEK1/2 inhibitors. These effects could be considered relevant in humans. The applicant will collect calcium and phosphate from ongoing selumetinib clinical studies and will monitor calcium and phosphate elevations during routine pharmacovigilance. Renal events will be closely monitored in paediatric patients.

The toxicological profile of selumetinib largely reflects the pharmacological action of the compound and is consistent with the reported findings for other marketed MEK1/2 inhibitors.

Aneugenic effects of selumetinb are known as pharmacological action of MEK inhibitors. However, no neoplastic changes were observed in carcinogenicity studies supporting the long-term treatment of children with selumetinib.

Selumetinib showed teratogenicity in an embryo-toxicity study in mice at clinically relevant plasma exposures. A second species was not used for investigating the potential effects on embryo-foetal development, which is acceptable in view of the toxicological findings reported in mice (embryolethality, teratogenicity). The available data in mice point to potential adverse effects on embryo-foetal and post-natal development at non-maternotoxic dose levels. Treatment-related external malformations (open eye) were reported at subclinical exposures, while there were safety margins of 3.5 to the clinical free Cmx for embryolethal and foetotoxic effects. Pups exposed during gestation and lactation at 6-fold clinical exposure (total Cmax) were shown to be affected by reduced growth and decreased ability to meet the criterion for pupil constriction at weaning.

No specific juvenile toxicity studies have been conducted but studies performed in sexually immature primates and younger mice cover the age of children from 12 years onwards. Therefore, concerning pharmacokinetics, exposure assessments at dose levels investigated in adults are considered to be sufficient to evaluate exposures expected in the younger population, e.g. from 3 years onwards.

Selumetinib was positive in the mouse micronucleus study via an aneugenic mode of action. The free mean exposure (C_{max}) at the no observed effect level (NOEL) was approximately 27-times greater than clinical free exposure at the maximum recommended human dose (MRHD) of 25 mg/m^2.

Selumetinib is genotoxic and transfers into breast-milk of lactating mice at concentrations approximately the same as in plasma of dams. Breast-feeding should be discontinued during treatment with selumetinib.

In reproductive studies in mice, no effect on male or female fertility were reported.

Several impurities have been tested for their genotoxic potential and are controlled in the manufacturing process in accordance with ICH M7(R1).

Selumetinib was not carcinogenic in rats or transgenic mice.

Selumetinib does not present any phototoxic potential based on the results of the phototoxicity study.

Considering the provided ecotoxicological data, selumetinib is not expected to pose a risk to surface water, groundwater and sediment. The active ingredient selumetinib formed a potentially very persistent transformation product in water sediment systems and during transformation in sewage sludge. A terrestrial risk assessment was not required as the trigger value for adsorption to sewage sludge is not exceeded. The provided data on logDow in Phase I is suitable to derive the conclusion

that selumetinib does not meet the PBT characteristics. In conclusion, selumetinib is not expected to pose a risk to the environment when used in accordance with the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted support the use of selumetinib in the intended indication. The MAH is recommended to submit the final audited GLP AMES report with AZ11129886 (4-bromo-2-chloroaniline) (study 8466469) as soon as the report is available.

Based on a complete Phase II assessment it can be concluded that no environmental effects are expected following the use of selumetinib.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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

Study number (acronym)	**Patient Population**	**Selumetinib Treatment Regimen**	**Number of patients randomised/ treated in study**	**Number of patients included for Efficacy**	**Number of patients included for Safety**		**Design**	**Primary Endpoint**	**No. of study centres / locations**
					Capsule (Hydsulfate)	**Free-base**			
Pivotal data (providing pivotal efficacy, clinical pharmacology, and safety data):									
D1532C00057 (**SPRINT Phase II Stratum 1**; NCT01362803)	Patients aged ≥2 and ≤18 years with NF1 and inoperable PN[a], with PN-related morbidity at the time of enrolment	Selumetinib 25 mg/m^2 BID continuously for 28-day cycles with no rest periods between cycles.	50/50	50	50	-	Non-comparative	**ORR**	4 US study sites
External Control Data (providing context for efficacy of pivotal data):									

Study number (acronym)	Patient Population	Selumetinib Treatment Regimen	Number of patients randomised/ treated in study	Number of patients included for Efficacy	Number of patients included for Safety		Design	Primary Endpoint	No. of study centres / locations
					Capsule (Hyd sulfate)	Free-base			
Pivotal data (providing pivotal efficacy, clinical pharmacology, and safety data):									
01-C-0222 (Placebo arm of **tipifarnib study**, Phase A only, NCT00021541)[b]	Children and young adults (≥3 and ≤25 years) with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity	NA	29 in the placebo arm in Phase A	29	NA	-	Comparative	**TTP**	10 participating US sites, of which 7 enrolled patients
NCI-08-C-0079 (**NH study**, NCT00924196)[b]	Paediatric and adult patients ≤35 years old NF1 or a confirmed NF1 mutation from ongoing NF1 clinical studies	NA	92-111 with NF1-related PN	92-111	NA	-	Non-comparative	To longitudinally characterize and analyse NF1-related tumour and non-tumour manifestations (e.g. to for **PN**s analyse **growth rate over time**)	1 US study site
Supportive Phase I (providing supportive efficacy, clinical pharmacology, and safety data):									
D1532C00057 (**SPRINT Phase I**, NCT01362803)	Patients aged ≥3 and ≤18 years (able to swallow whole capsules) with NF1 and inoperable PN	Selumetinib 20, 25, and 30 mg/m^2 BID continuously for 28-day cycles.	24/24	24	24	-	Non-comparative	MTD and RP2D, and to study PK **Key secondary: percentage PN volume change**	4 US study sites
TOTAL: Paediatric Pool (Phase II Stratum 1 and Phase I)					**74**				
Supportive studies in adult patients with other tumour types (providing supportive safety and clinical pharmacology data):									

Study number (acronym)	Patient Population	Selumetinib Treatment Regimen	Number of patients randomised/ treated in study	Number of patients included for Efficacy	Number of patients included for Safety		Design	Primary Endpoint	No. of study centres / locations	
					Capsule (Hyd sulfate)	Free-base				
Pivotal data (providing pivotal efficacy, clinical pharmacology, and safety data):										
D1532C00005 (Phase I)	Adult patients with advanced solid malignancies	Part A: 25, 50, 75, 100 mg BID Hyd-Sulfate capsule Part B: 75 mg Hyd-Sulfate capsule vs 100 mg free base	60/56	NA	34	-				
D1532C00020 (Phase I)	Adult patients with advanced solid malignancies	75 mg BID	31/30	NA	30	-				
D1344C00001 (Phase III) (SUMIT)	Adult patients with metastatic uveal melanoma receiving first-line treatment	Selumetinib 75 mg BID	129/114[c]	NA	15[d]	-				
D1532C00003 (Phase II)	Adult patients with unresectable AJCC Stage 3 or 4 malignant melanoma	Selumetinib 100 mg BID	194/158[e]	NA	-	158				
D1532C00008 (Phase II)	Adult patients with advanced or metastatic pancreatic cancer, failed first-line gemcitabine therapy	Selumetinib 100 mg BID orally for 2 weeks, followed by a 1-week rest period.	70/69	NA	-	37				
D1532C00011 (Phase II)	Adult patients with colorectal cancer, failed at least 1 prior chemotherapy regimen	Selumetinib 100 mg BID vs capecitabine 1250 mg/m^2 BID	69/68	NA	-	34				

Study number (acronym)	Patient Population	Selumetinib Treatment Regimen	Number of patients randomised/ treated in study	Number of patients included for Efficacy	Number of patients included for Safety		Design	Primary Endpoint	No. of study centres / locations	
					Capsule (Hyd sulfate)	Free-base				
Pivotal data (providing pivotal efficacy, clinical pharmacology, and safety data):										
D1532C00012 (Phase II)	Adult patients with NSCLC, failed 1 or 2 prior chemotherapy regimens	Selumetinib 100 mg BID vs. pemetrexed 500 mg/m^2	84/84	NA	-	39				
TOTAL: Adult monotherapy Hyd-sulfate capsule					**N = 79**					
TOTAL: Adult monotherapy free-base						**N=268**				
TOTAL: Adult Monotherapy pool (all 7 studies)					**N=347 (79+268)**					

[a] Defined as PN that cannot be surgically completely removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN.

[b] A summary of the tipifarnib study and the NH study were provided.

[c] Includes 97 patients who received randomised treatment with selumetinib+dacarbarbazine, plus 17 patients randomised to placebo+dacarbazine who received open-label selumetinib (or selumetinib+dacarbazine) after disease progression.

[d] The 15 patients included in the adult monotherapy Hyd-Sulfate sub-group comprise 5 patients randomised to selumetinib+dacarbazine plus 10 patients randomised to placebo+dacarbazine, who all received open-label selumetinib post treatment discontinuation.

[e] Includes 99 patients who received randomised treatment with selumetinib, plus 59 patients randomised to temozolomide who subsequently crossed over to receive selumetinib.

AJCC American Joint Committee on Cancer; BID Twice daily; CSR Clinical Study Report; MTD maximum tolerated dose; NA Not applicable; NCI National Cancer Institute; NH Natural History; NF1 Neurofibromatosis type 1; NSCLC Non-small cell lung cancer; ORR Objective response rate; PK Pharmacokinetics; PN Plexiform neurofibroma(s); POB Pediatric Oncology Branch; RP2D Recommended Phase II dose; TTP Time to progression.

Additionally, the clinical pharmacology investigations of selumetinib and its active metabolite (N-desmethyl selumetinib) are presented in Table 9.

Table 4: Clinical Pharmacology studies

D1532C00005	A Phase I, Open-Label, Multi-centre Study to Assess the Safety, Tolerability and Pharmacokinetics of a Solid Oral Dosage Formulation (capsule) of AZD6244 in Patients with Advanced Solid Malignancies
D1532C00020	A Phase I, Open-Label Study to Assess the Effect of Dosing AZD6244 Hyd-Sulfate in the Presence and Absence of Food in Patients With Advanced Solid Malignancies
D1532C00066	A Phase I, Single-center, Randomized, Open-label, Crossover Study to Compare the White (Current Phase II) and Blue (Planned Phase III) Capsule Formulations of AZD6244 Hyd-Sulfate in Healthy Male Subjects
D1532C00069	A Phase I, Randomized, Open-label, Single-center, Crossover Study to Assess the Effect of Food on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib in Healthy Male Volunteers Aged 18 to 45 Years
D1532C00071	A Phase I, Double-blind (Selumetinib [AZD6244; ARRY-142886] [Hyd-Sulfate]), Placebo-controlled, Open-Label (Moxifloxacin) Positive-controlled, Randomized, Three-period Crossover Study to Assess the Effects of Single Oral Dose of Selumetinib (75 mg) on QTc Interval Compared to Placebo, using AVELOX (Moxifloxacin) as a Positive Control, in Healthy Male Volunteers Aged 18 to 45 years
D1532C00077	A Phase I, Single-centre, Non-randomised, Open-label, Pharmacokinetic and Mass Balance Study of Orally Administered [^{14}C]-selumetinib in Healthy Male Volunteers
D1532C00078	A Phase I, Single centre, Randomised, Open label, Crossover Study to Assess the Bioequivalence or Relative Bioavailability of Variants of Selumetinib (AZD6244, Hyd-Sulfate) Blue Capsules in Healthy Male Volunteers Aged 18 to 45 years
D1532C00080	A Study to Assess the Absolute Bioavailability of a Single Oral Dose of Selumetinib with Respect to an Intravenous Microdose of [^{14}C] selumetinib in Healthy Male Volunteers
D1532C00081	An Open-label Comparative Study of the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY-142886) (Hyd-Sulfate) following a Single Oral Dose in Subjects with Renal Impairment and Healthy Subjects
D1532C00082	An Open-label, Comparative Study to Assess the Pharmacokinetics, Safety and Tolerability of Selumetinib (AZD6244, ARRY-142886) (Hyd-Sulfate) following Single Oral Dosing to Healthy Subjects and to Subjects with Mild, Moderate, and Severe Hepatic Impairment
D1532C00083	A Phase I, Open-label, Single-center Study to Assess the Effect of the CYP3A4 Inhibitor Itraconazole and the CYP2C19 Inhibitor Fluconazole on the Pharmacokinetics of a 25 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142866) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years
D1532C00085	A Phase I Open-label, Single-center Study to Assess the Effect of the CYP3A4 inducer Rifampicin on the Pharmacokinetics of a 75 mg Single Oral Dose of Selumetinib (AZD6244; ARRY-142886) (Hyd-Sulfate) in Healthy Volunteers aged 18 to 45 years
D1532C00086	A Phase I, Single-centre, Open-label, Dose-escalation Study to Assess the Safety, Tolerability and Pharmacokinetics of Selumetinib Given Orally in Japanese and Non-Japanese Asian Healthy Male Volunteers
D1532C00089	A Phase I, Open-label, Single-center Relative Bioavailability and Food Effect Randomized Crossover Study of New Granule and Capsule Formulations of Selumetinib (AZD6244) in Healthy Male Subjects

2.4.2. Pharmacokinetics

Full PK profiling has been performed in healthy volunteers whereas rich and sparse PK sampling were performed in adult and pediatric patients. Pooled PK data from both adult and pediatric patients and healthy subjects were used to develop a Population PK model and Exposure-response analysis as presented in Table 10.

Table 5: Modelling and PK/PD studies

C-QTc report	PK-PD Analysis to Evaluate the Potential Effect of Selumetinib on QTcF Interval
MS-01 report	Selumetinib Population Pharmacokinetic Modelling and PK/PD Modelling Analysis
MS-02 report	Physiologically Based Pharmacokinetic Modelling using Simcyp® (version 17) to Evaluate Potential Drug-Drug Interactions with Selumetinib
MS-03 report	Physiologically Based Pharmacokinetic Modelling using Simcyp® to Identify Dose in Paediatric Subjects for Selumetinib

Bioanalysis

Throughout the clinical development, different bioanalytical methods were used to quantify selumetinib and its active metabolite N-desmethyl selumetinib in human plasma with K2EDTA as anticoagulant. The method 244HHP was used to support the pivotal paediatric study 057 (SPRINT) and two phases 1 studies in healthy volunteers (ADME study 077 and relative bioavailability study 066), whereas method ANAHPP was used to support most of phase I studies in adult's healthy volunteers performed in adults and methods WMTD070, WMTD133 were used exclusively for adults' patients. These methods (including 244HHP in the target paediatric population) allows quantification of selumetinib over a concentration range of 2 ng/mL (LLoQ) to 2000 µg/mL and over a range of 2 to 500 ng/mL for N-desmethyl selumetinib in plasma samples.

Pharmacokinetic analysis

For single or multiple-dose studies, PK parameters evaluated in plasma include Cmax, Tmax, AUC_{0-t}, AUC_{0-12}, $AUC_{0-\infty}$, $AUC_{\%extra}$, R_{AUC}, T1/2, λz, CL/F, Vz/F, Vss/F, MAT, MRT, MR_{AUC}, MR_{Cmax}, CL, Vss, Vz PK parameters evaluated in urine include Ae, CLr, and fe.

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters.

A Population (Pop) PK analysis was performed based on data collected over 13 clinical studies (10 Phase I studies in healthy subjects, 2 Phase I monotherapy studies in patients with advanced cancer and 1 Phase I/II study in children and young adults with NF-1 and inoperable PN (pivotal study D1532C00057, SPRINT).

Plasma concentration-time data were analysed using a non-linear mixed effects modelling approach (non-linear mixed effects modelling software [NONMEM], Version 7.3 or greater). Post-processing of NONMEM analysis results was carried out in R version 3.2.4 or greater. The first-order conditional estimation method with between and within subjects random effect interaction (FOCE INTER) was used for NONMEM computations. NONMEM run execution, bootstrap, VPC, automated SCM building was carried out using PsN, version 4.4 or greater.

Absorption

Selumetinib

Following single or multiple-dosing of selumetinib at doses between 25 mg to 75 mg in adults the median T_{max} was 1 to 1.5h (Studies D1532C00005, D1532C00083, D1532C00082, D1532C00081, D1532C00089, D1532C00066, D1532C00078, D1532C00080, D1532C00069, D1532C00071, D1532C00085, D1532C00020).

After a single dose of 75 mg, in healthy volunteers Cmax ranged from 1150 ng/mL to 1520 ng/mL, in adult patients Cmax ranged from 1207 to 1365 ng/mL. After multiple dose of 75 mg in adult patients, $C_{max,ss}$ was 1439 ng/mL (29% CV).

In the pediatric patients, after single dose of selumetinib from 20 to 30 mg/m2, PK parameters are presented in Table 11 below.

Table 6: Selumetinib PK parameters in paediatric patients after single dose in SPRINT study (phase 1 and 2).

	Paediatric patients with NF1 (SPRINT Phase I & II)						
Dose (mg/m^2)	N	C_{max} (ng/mL) (GCV%)[a]	t_{max} (h) (range)[b]	AUC (ng*h/mL) (GCV%)[a]	CL/F (L/h) (SD)[c]	Vz/F (L) (SD)[c]	$t_{1/2}$ (h) (SD)[c]
20	9	755 (48)	1 (0.98-3.0)	2231 (18)	11.5 (5.1)	146 (62.4)	9.4 (4.6)
25	4	928 (18)	1 (1-2)	2550 (14)	8.8 (2.5)	78 (20.6)	6.2 (0.9)
30	5	963 (51)	1 (1-2)	3055 (39)	15.0 (7.5)	171 (121.0)	7.3 (6.9)
25 Phase II	50	731 (62)	1.5 (0.5-6)	2009 (35)[d]	NC	NC	NC

a. Geometric mean, GCV% geometric coefficient of variation, b Median (range), c Arithmetic mean (SD), d AUC0-12

At the recommended dose of 25 mg/m2 in the pediatric patients, geometric mean Cmax was estimated at 731 ng/mL with a median Tmax of 1.5 h.

N-desmethyl selumetinib

In the SPRINT Phase I/II study (paediatric patients) and in healthy volunteers, the median Tmax of the active metabolite N-desmethyl selumetinib was rapid and ranged from 1 to 1.5 h.

Following a single 75 mg dose of selumetinib capsules to healthy volunteers and adult patients, the geometric mean Cmax of N-desmethyl selumetinib ranged from 88 to 106 ng/mL and 67 to 78 ng/mL.

In the pediatric patients, after single dose of selumetinib from 20 to 30 mg/m2, PK parameters of N-desmethyl selumetinib are presented in Table 12 below.

Table 7: N-desmethyl selumetinib metabolite PK parameters in paediatric patients after single dose in SPRINT study

Paediatric patients with NF1 (SPRINT Phase I)							
Dose (mg/m^2)	N	C_{max} (ng/mL) (GCV%)[a]	t_{max} (h) (range)[b]	AUC (ng*h/mL) (GCV%)[a]	MPR C_{max} (GCV%)[a]	MPR AUC (GCV%)[a]	$t_{1/2}$ (h) (SD)[c]
20	9	58 (71)	1 (0.98-3)	205 (37)	0.08 (30)	0.08 (31)	9.4 (10.2)
25	4	56 (35)	1 (1-2)	177 (26)	0.06 (39)	0.06 (31)	4.5 (2.5)
30	5	57 (49)	1(1-2)	200 (28)	0.06 (59)	0.06 (53)	7.0 (3.9)
25 Phase II	50	54 (60)	1.5 (0.5-6)	169 (29)[d]	0.07 (28)	0.08 (24)	NC

a Geometric mean, GCV% geometric coefficient of variation, b Median (range), c Arithmetic mean (SD), d AUC0-12

At the recommended dose of 25 mg/m2 in the pediatric patients, geometric mean Cmax of N desmethyl selumetinib was estimated at 54 ng/mL with a median Tmax of 1.5 h.

Absolute bioavailability

The absolute bioavailability of selumetinib was estimated at around 62.1% (90% CI: 60.1 - 64.1) following an oral dose of 75 mg selumetinib capsule formulation (3x25 mg) in the fasted state and intravenous administration of approximately 80 µg (~ 1 µCi) of [14C]-selumetinib.

Metabolite ratio based on AUC or Cmax was 7.68% and 6.32% respectively.

Relative bioavailability /Bioequivalence

Two selumetinib capsule strengths (10 mg white and 25 mg blue) have been used in the SPRINT clinical study.

However, initially a 25 mg white capsule was developed and used during the adult patient study D1532C00005. Then a 25 mg blue capsule was introduced during this study. The 25 mg blue capsule was used in all the studies pertaining to the clinical pharmacology program. In order, to bridge the two 25 mg capsules (white and blue), a relative bioavailability study (Study D1532C0066) was performed from which results demonstrated similarity in terms of AUC only with a 90% CI geometric LS mean ratio of 80.09-100. For Cmax, the 90% CI for the geometric LS mean ratio was 71.75-102.32%.

Influence of food

In study DC1532C0069, the effect of a high fat meal on selumetinib PK was investigated in 32 healthy volunteers who were administered a single oral dose of 75 mg selumetinib in the fasted and the fed states. PK results indicated that administration of a high fat meal delayed the absorption of selumetinib and N-desmethyl selumetinib with median Tmax delayed from 1h in the fasted state to 2.5 h in the fed state. In the fed state the AUC and Cmax of selumetinib was 16% and 50% lower compared to the fasted state. For N-desmethyl selumetinib the AUC and Cmax decreased similarly by 14% and 47% respectively.

In study DC1532C00020, the effect of a high fat meal on selumetinib PK was investigated in 34 adult patients who were administered a single oral dose of 75 mg selumetinib in the fasted and the fed states. PK results indicated that administration of a high fat meal delayed the absorption of selumetinib and N-desmethyl selumetinib with median Tmax delayed from 1h in the fasted state to 4 h in the fed state. In the fed state the AUC and Cmax of selumetinib was 19% and 62% lower compared to the fasted state.

In study DC1532C0089, the effect of a low fat meal on selumetinib PK was investigated in 24 healthy volunteers who were administered a single oral dose of 50 mg selumetinib capsule in the fasted and the fed states. PK results indicated that administration of a low fat meal delayed the absorption of selumetinib and N-desmethyl selumetinib with median Tmax delayed from 1.15h in the fasted state to 2 h in the fed state. In the fed state the AUC and Cmax of selumetinib was 38% and 60% lower compared to the fasted state.

Distribution

Based on *in vitro* investigations (Study KPJ003), Selumetinib was found to be highly bound (98.4%) to human plasma proteins. The unbound fraction was independent of selumetinib concentration. In addition, selumetinib mostly binds to serum albumin (96.1%) compared to α-1 acid glycoprotein (< 35%). N-desmethyl selumetinib was also found to be highly bound (97.9%).

In the human AME study (Study D1532C0077), the blood-to-plasma radioactivity ratios was determined to be 0.6-0.69, suggesting lack of meaningful distribution of Selumetinib into blood cells. Based on *in vitro* investigation (Study KPJ003), B/P ratio ranged from 0.55-0.71.

Following IV dosing, in healthy volunteers the selumetinib volume of distribution at steady state in plasma was 59.8 L, whereas following oral dosing the apparent distribution volume was 170 L, thus indicating high distribution in tissues.

Following oral dosing in adult patients with advanced solid malignancies (Study DC15320005) Vss/F ranged from 89 to 125 L after a 75 mg dose.

In paediatric patients Vz/F ranged from 78 to 171 L with dose ranging from 20 to 30 mg/m^2, in line with the results obtained in healthy volunteers and adult patients.

Elimination

The excretion and biotransformation of [14C]-selumetinib were investigated in a formal AME study (D1532C0077) in 6 male healthy subjects following a single oral dose of 75 mg selumetinib (3x25 mg capsule) incorporating 610 µCi of [14C]-selumetinib.

The overall recovery of radioactivity was high (92.8% ± 1.09%), with 59.3% ± 10.2% of the dose recovered in faeces and 33.8 % ± 8.49% recovered in urine. Approximately 19% of [^{14}C]-AZD6244 was recovered unchanged in faeces, whereas less than 1% was recovered unchanged in urine. (see Figure 2)

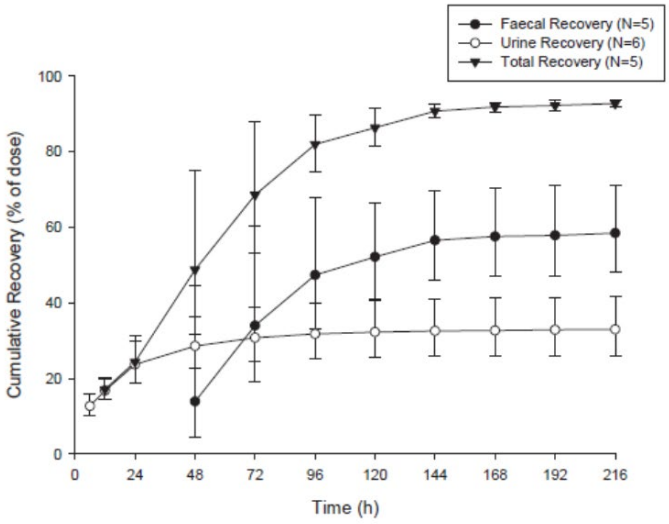


Figure 2: Mean cumulative excretion, in percentage of radioactive dose, in urine and faeces following an oral dose of 75 mg 14C- selumetinib

Metabolite profiling was performed (Study YAU69) following oral dose and more than 90% and 83% of the recovered radioactivity in urine and faeces respectively was identified.

Selumetinib appears to undergo extensive metabolism (Figure 3). Renal clearance of selumetinib was estimated at 0.084-0.093 L/h (Study D1532C0081, D1532C0082) and 1.54-2.15 L/h for N-desmethyl selumetinib.

Fifteen (15) metabolites were identified in plasma, urine and feces.

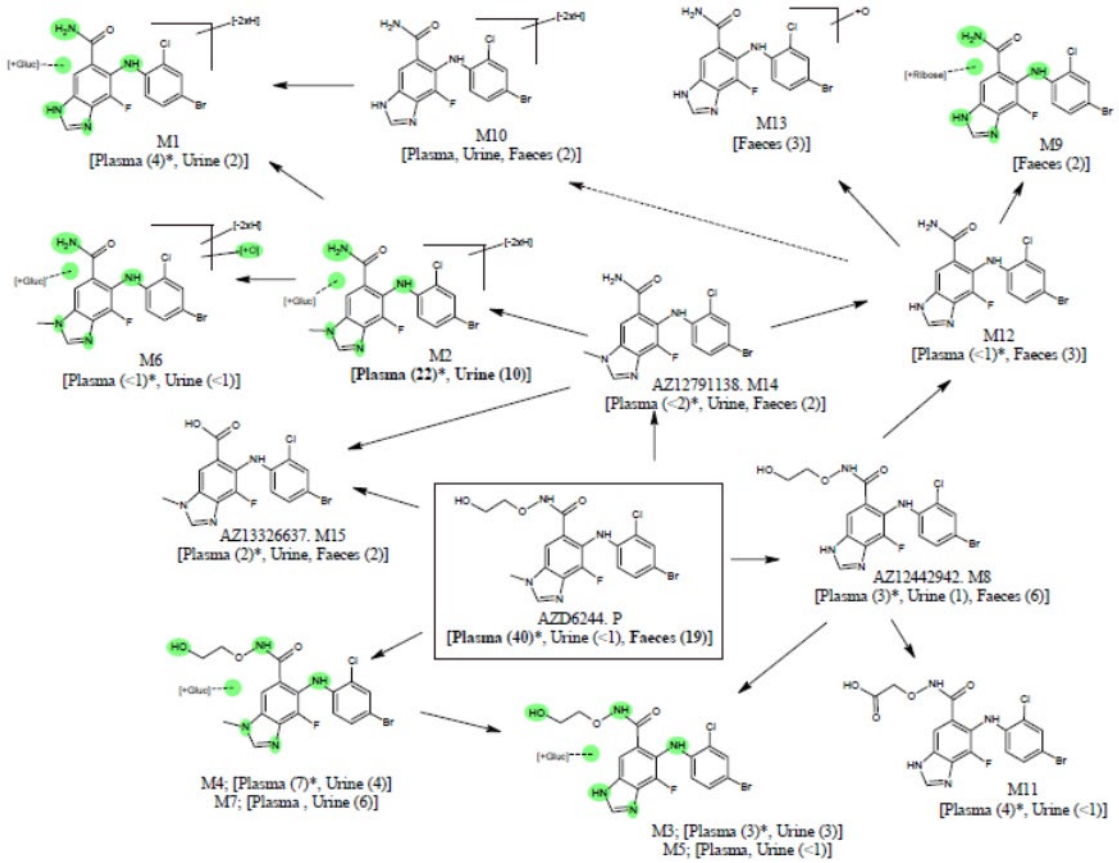


Figure 3: Proposed metabolic pathways of selumetinib

Based on *in vitro* investigations using human recombinant CYP enzymes (Study BS001696-61), selumetinib was found to be predominantly metabolized by CYP3A4 (85%) and to a lesser extent by CYP3A5, 2C19, 2D6, 2C9 and 2E1. M8 (N-desmethyl selumetinib) formation is predominantly mediated by CYP2C19 with lesser contributions from CYP1A2, 2A6 and 2C9. Glucuronidation is a significant route of elimination for selumetinib phase 1 metabolites to form glucuronide conjugates involving several UGT isoforms (mainly UGT1A1 and 1A3).

Overall the relative contribution of CYP and UGT were 56% and 29% respectively based on in vitro data.

In addition, Selumetinib showed no inhibition on CYP1A2, 2A6, 2C8, 2C19 and 2E1, , but was found to be a weak inhibitor of CYP2C9, 2B6, 2D6 and 3A4. Time dependent inhibition at 10 to 50 µM was not observed for 2C8, 2C9, 2D6 and 3A4/5. Weak time dependent inhibition at 50 µM was observed with CYP1A2, 2B6 and 2C19.

In adult patients, the mean terminal half-life ranged from 5.3 to 7.8 h. In healthy volunteers, across the studies, mean terminal half-life ranged from 4 to 21 hours across the dose range of 25 mg to 75 mg.

In pediatric patients at the recommended dose of 25 mg/m2 (see Table 13), mean terminal half-life was estimated at 6.2 h.

The mean apparent clearances (CL/F) for selumetinib in healthy volunteers ranged from 15.5 to 21.1 L/h. In adult patients after MD of 75 mg BID, CL/F ranged from 12.2 to 18.8 L/h.

In pediatric patients, at the recommended dose of 25 mg/m2, CL/F was estimated at 8.8 L/h.

Pharmacokinetic of metabolites

Following oral dosing of ^{14}C-selumetinib to healthy male subjects, unchanged selumetinib (~40% of the radioactivity) with other metabolites including glucuronide of imidazoindazole metabolite (M2; 22%), selumetinib glucuronide (M4; 7%), N-desmethyl selumetinib (M8; 3%), and N-desmethyl carboxylic acid (M11; 4%) accounted for the majority of the circulating radioactivity in human plasma. N-desmethyl selumetinib represents less than 10% of selumetinib levels in human plasma but is approximately 3 to 5 times more potent than the parent compound, contributing to about 21% to 35% of the overall pharmacologic activity.

Across all the studies in adult, metabolite to parent ratio ranged from 5.9 to 7.7%. In pediatric subjects, at steady state, conversion to the N-desmethyl selumetinib from parent was low with with geometric mean metabolite to parent ratios of 6.06% for Cmax and 6.52% for AUClast, respectively.

Dose proportionality and time dependencies

Dose proportionality

Based on pooled PK data from healthy volunteers, dose proportionality was observed from 25 mg to 75 mg, with estimated slope of 0.99 and 1.01 respectively for AUC and Cmax, using a power model.

In adult patients, from 25 mg to 100 mg, Cmax and AUC increased dose proportionally. For paediatric patients, an increase in selumetinib exposure (AUC) from 20 mg/m² to 25 mg / m² dose, from 25 mg/ m² to 30 mg/m² dose, and from 20 mg/m² to 30 mg/ m² dose was 1.19, 1.09 and 1.3, respectively (study SPRINT).

Time dependency

Only patients received multiple dose of selumetinib, therefore information on time dependency was retrieved from Study D1532C00005 and the SPRINT study.

For adult and paediatric patients, based on the terminal half-life, steady state would be expected to be achieved after 3 days of BID dosing. In Study D1532C00005, AUC for selumetinib was similar after single (Day 1) and multiple (Day 8) dosing over time after BID dosing, consistent with the terminal half-life observed (AUC ratio Day 8/Day 1 ~1.2 to 1.5 at all doses in study D1532C00005).

Inter and Intra-individual variability

Assessment of intra-subject and IIV for Cmax and AUC from single doses of 75 mg selumetinib was determined in study D1532C0066. Cmax and AUC intra-subject variability was 34% and 17% respectively. Across patients studies, IIV in exposure was moderate to high, with %CV of 40 to 68%, and 26 to 50% for Cmax and AUC respectively. In healthy subjects, IIV in exposure was marginally less variable, with 33 to 48%, and 20 to 32.5% for Cmax and AUC respectively. In paediatric patients at 25 mg/m², IIV of AUC and Cmax were 35 and 62%, respectively.

Pharmacokinetics in target population

In paediatric patients, after single dose of 25 mg/m2 the geometric mean AUC was 2009 ng.h/mL. Minimal accumulation of ~1.1 fold was observed at steady state upon twice daily dosing.

Special populations

Evaluation of selumetinib PK in special populations was based either on formal dedicated PK studies or on the PopPK analysis.

Impaired hepatic function

A formal dedicated study (D1532C0082) investigating the effect of various degree of hepatic impairment according to the Child-Pugh classification on PKs of selumetinib was performed.

Adult subjects with normal hepatic function (n = 8) and mild hepatic impairment (Child-Pugh A, n = 8) were dosed with 50 mg selumetinib, subjects with moderate hepatic impairment (Child-Pugh B, n = 8) were administered a 50 or 25 mg dose, and subjects with severe hepatic impairment (Child-Pugh C, n = 8) were administered a 20 mg dose. Selumetinib total dose normalised AUC and unbound AUC were 86% and 69% respectively, in mild hepatic impairment patients, compared to the AUC values for subjects with normal hepatic function. Selumetinib exposure (AUC) was higher in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment; the total AUC and unbound AUC values were 159% and 141% (Child-Pugh B) and 157% and 317% (Child-Pugh C), respectively, of subjects with normal hepatic function (see SmPC section 4.2). There was a trend of lower protein binding in subjects with severe hepatic impairment although the protein binding remained > 99% (see SmPC section 4.3).

PK data from specific cohorts including PK data in mild, moderate and severe hepatic impairment patients from the dedicated study D1532C0082 were excluded from the Pop PK analysis.

Impaired renal function

A formal dedicated study (D1532C0081) investigating the effect of various degree of renal impairment on PKs of selumetinib was performed.

The exposure of 50 mg oral selumetinib was investigated in adult subjects with normal renal function (n = 11) and subjects with end stage renal disease (ESRD) (n = 12). The ESRD group showed 16% and 28% lower Cmax and AUC, respectively, with the fraction of unbound selumetinib being 35% higher in ESRD subjects. As a result, the unbound Cmax and AUC ratios were 0.97 and 1.13 in the ESRD group when compared to the group with normal renal function. A small increase, approximately 20% AUC, in the N-desmethyl metabolite to parent ratio was detected in the ESRD group when compared to the normal group.

PK data from specific cohorts including PK data in end stage renal disease patients from the dedicated study D1532C0081 were excluded from the Pop PK analysis.

Gender

No formal PK study to investigate the effect of gender on the PKs of selumetinib and/or its active N-desmethyl metabolite was submitted. The effect of gender on the PKs of selumetinib was investigated in patients based on the Pop PK approach.

Based on the results of the final Pop PK model, gender was not found to have an effect on PK parameters of selumetinib and/or its active N-desmethyl metabolite.

Race

A formal dedicated study (D1532C0086) investigating the effect of race (Asian) on PKs of selumetinib was performed.

The geometric mean ratio (90% CI) of the AUC and Cmax normalised by dose and body weight between Chinese and Western population were 1.19 (1.03, 1.38) and 1.17 (0.92, 1.48), respectively. Similarly, the differences of mean PK exposure (AUC and Cmax) between Japanese and Western subjects were reduced from approximately 1.6-1.8-fold higher to approximately 1.4- to 1.7-fold higher after body weight or BSA normalization.

Based on the results of the final Pop PK model, race was found to have a significant effect covariate on selumetinib CL and consequently on the systemic exposure (AUCss) with a 19% reduction for Asians compared to non-Asians.

Weight/BSA

The effect of weight on the PKs of selumetinib was investigated in paediatric patients based on a pooled Pop PK analysis.

BSA was identified as a significant covariate impacting clearance (CL) and volumes of distribution (V2 and V3) for selumetinib and Fm/V4 parameter for N-desmethyl selumetinib and therefore retained in the final Pop PK model. BSA was related to CL, V2, V3 and Fm/V4 following estimated exponents of 0.97, 1.57, 0.97, -1.0, respectively, where selumetinib clearance (parameter driving exposure) increases proportionally to BSA (exponent is 0.97). For a typical child 10 years old, CL decreases by more than 30% with a BSA 0,7 m² (extreme low 5% of the observed BSA distribution) by comparison to the typical value of CL observed with a reference BSA of 1m². In contrast, CL increases by 75% with a BSA of 1,83 m² (extreme upper 95% of the observed BSA distribution) by comparison to the typical value of CL observed with a reference BSA of 1m².

Based on these findings, an individualised dose based on BSA was proposed in paediatrics. Among the 3 levels of doses tested in the SPRINT Phase I study, the 30 mg/m² BID dose was declared as not tolerated clinically (see section 2.5.1). Then, the 25 mg/m² BID dose was identified as the recommended dose in paediatric patients. The posology of BSA based dosing is shown in Table 13.

Table 8: Dosing scheme of selumetinib 25 mg/m² twice daily.

BSA	Recommended dosage	BID dose level (mg/m^2)	Total daily dose level (mg/m^2)
0.55-0.69 m^2	20 mg in the morning and 10 mg in the evening	N/A	43.5-54.5
0.70-0.89 m^2	20 mg BID	22.5-28.6	44.9-57.1
0.90-1.09 m^2	25 mg BID	22.9-27.8	45.9-55.6
1.10-1.29 m^2	30 mg BID	23.3-27.3	46.5-54.5
1.30-1.49 m^2	35 mg BID	23.5-26.9	47.0-53.8
1.50-1.69 m^2	40 mg BID	23.7-26.7	47.3-53.3
1.70-1.89 m^2	45 mg BID	23.8-26.5	47.6-52.9
> 1.90 m^2	50 mg BID	< 26.3	< 52.6

BID = Twice daily; BSA = Body surface area; N/A = not applicable

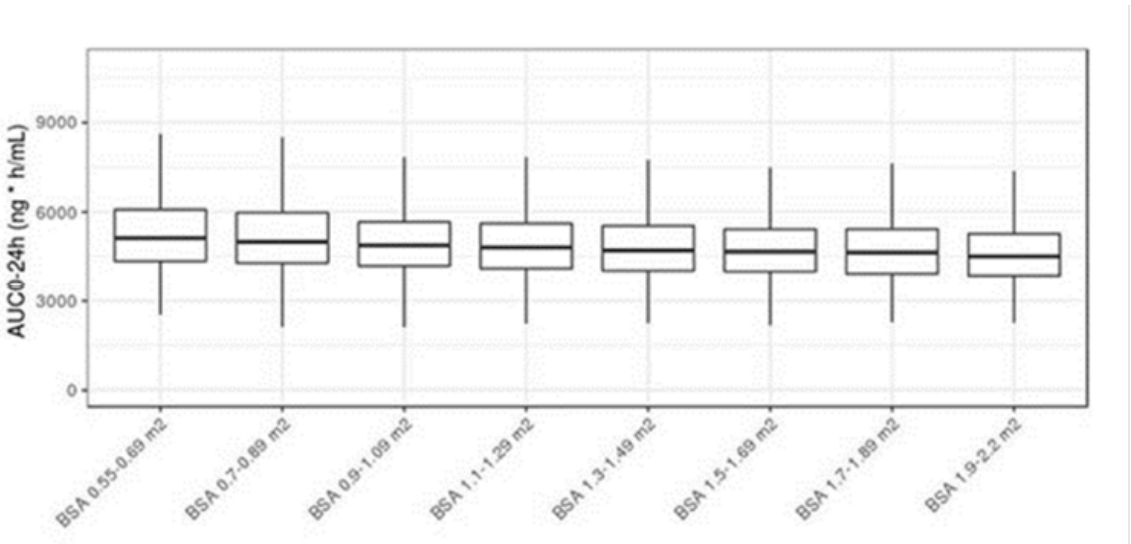


Figure 4: Simulated steady-state AUC0-12h following 25 mg/m² nomogram summarised per BSA band

The final Pop PK model was used to simulate 1000 individual steady-state AUC0-12h for each BSA band in paediatric patients aged 3 to 18 years old. The results are visualised in Figure 4.

Pharmacokinetic interaction studies

The ability of selumetinib to be a direct and time-dependent inhibitor of the main CYP enzymes CYP1A2, 2B6, CYP2C8, CYP2C9, 2C19, 2D6 and 3A4, with a range of concentrations from 0,05 to 70 µM, was investigated and results are presented below.

- CYPs inhibition by selumetinib

Results from studies KMX10, ADME-AZS-Wave3-150511 and ADMEAZS-Wave3-150512 show that, at the highest tested concentrations of 50µM and 70µM, direct inhibition by selumetinib was observed on CYP1A2, 2B6, CYP2C8, CYP2C9, 2C19, 2D6 and 3A4 but with IC50 values > 40µM. Notwithstanding the lack of Ki measure, this is far higher than the worst estimated concentrations of selumetinib at the systemic level, i.e. 1,2 µM and 1,75 µM for the dose of 25 mg and 50 mg, respectively.

As regards CYP3A4, according to results from study KMX010, an IC50 value could not be calculated whereas, from other studies ADME-AZS-Wave3-150511 and ADMEAZS-Wave3-150512, the estimation of R1gut =1 + [Igut]/Ki for both nifedipine and midazolam, provided a value of 13,5 which is superior to the cut-off value of 11, indicating drug-drug interaction (DDI) risk at the intestinal level cannot be ruled out.

Selumetinib is a time-dependent inhibitor for CYP1A2 and CYP2C19 with KI values=15,2 µM and 57,5 µM, respectively, which are higher than selumetinib worst expected concentrations at systemic level (i.e. 1,2 µM and 1,75 µM at the dose of 25 mg/m² and 50 mg/m² respectively).

No time-dependant inhibition (TDI) was observed on CYP2D6, CYP2C9 and CYP3A4 by selumetinib. Study BS002913-68 assessed the time-dependent inhibition potential of selumetinib toward CYP2B6 and CYP2C8. No TDI was observed against CYP2C8 but a minor effect was observed on CYP2B6 (25.7% TDI) at 50 µM. An additional investigation to better characterise this signal as part of a second *in vitro* study BS002913-81 was made and to estimate KI and K_{inact} for CYP2B6. Selumetinib exhibited a TDI *in vitro* with a KI=36µM and K_{inact}=0, 0165 min^{-1}.

CYPs inhibition by N-desmethyl metabolite

The potential for the N-metabolite to impact CYP activities (study KMX015) was investigated. Results showed that neither direct nor time-dependent inhibition due to the main selumetinib metabolite N-desmethyl are expected at clinically relevant concentrations.

CYP1A2, 2B6 and 3A4 induction by selumetinib

Two studies were carried out to assess the ability of selumetinib to induce CYP1A2, 2B6 and 3A4: KMX042 and study 1408211. The study KMX042 investigated selumetinib inducing potential by measuring enzyme activities.

The study 1408211 assessed selumetinib induction on CYP1A2, 2B6 and 3A4 in primary cultures of human hepatocytes by mRNA measurements. No signal of CYP1A2 and CYP2B6 induction was observed at concentrations expected at therapeutic level. For CYP2B6, conversely, a 2-fold increase of mRNA occurred at 100µM.

Based on the relative induction score (RIS) correlation method, selumetinib is a CYP3A4 inducer.

Impact on UGTs

Selumetinib is also glucuronidated by UGT1A1 and to a lesser extent by 1A3. Any inhibition or induction of these enzymes is expected to have an impact on selumetinib. A clinical DDI study has been performed with rifampicin (see *in vivo* part) but not with an inhibitor such as atazanavir or imatinib. The relative contribution to selumetinib turnover by CYP and UGT enzymes was investigated in cryopreserved human hepatocytes (Study BE000021-21). Results indicated that CYP mediated metabolites contributes 56% to the overall metabolism of selumetinib and UGT to 29%.

The impact of selumetinib on UGT1A3, UGT1A4, UGT1A6, and UGT1A9, was assessed through two *in vitro* DDI studies: BS002913-69 for UGT1A9 and BS002913-80 for UGT1A3, UGT1A4, and UGT1A6.

Based on the observed data, selumetinib inhibits UGT1A3, UGT1A4, UGT1A6, and UGT1A9 but their IC_{50} values of 24.7, 154, 126 µM and 235 µM, respectively, were far higher than the worst expected concentration at the systemic level considering results of the R value estimations ($[I_{max,u}] / K_i$) from the basic method.

Interactions related to efflux transporters and uptake transporters

In vitro studies suggest that selumetinib is a substrate for the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp) transporters and does not inhibit the P-gp but is a weak inhibitor of BCRP.

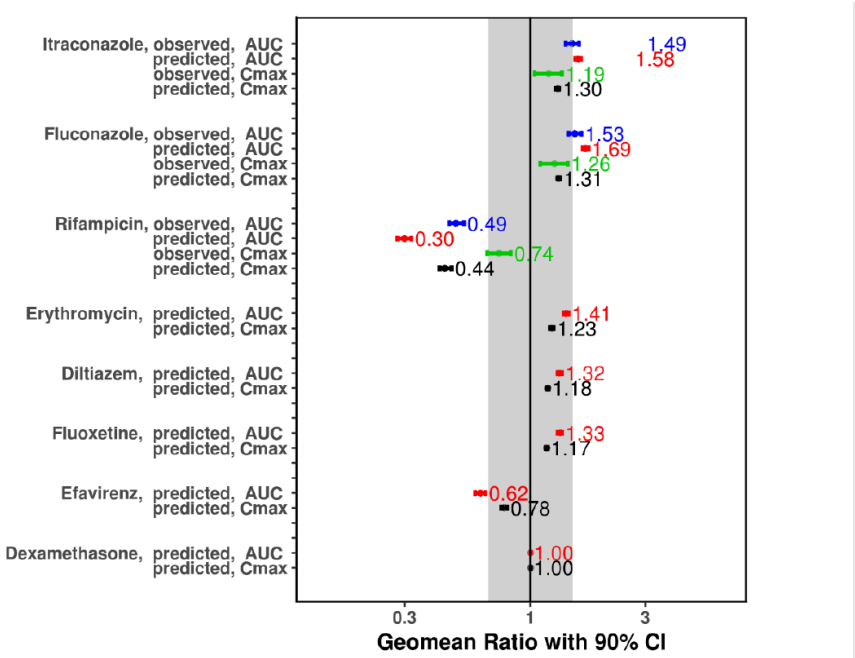
Selumetinib is not an OATP1B1 and OATP1B3 substrate. Selumetinib inhibited OATP1B1 and OATP1B3 with an IC50=8,76 µM and 19µM, respectively. IC50 values were upper than the worst expected concentrations at the portal vein level, i.e. 3,75 µM and 6,5 µM for the corresponding doses of 25 mg and 50 mg.

Selumetinib did not inhibit OCT1 at the tested concentrations and was not a substrate of this uptake transporter. The potential inhibitory effect of selumetinib on the renal uptake transporters OAT1, OAT3 and OCT2, and on the efflux transporters MATE-1 and MATE-2K was investigated. Selumetinib inhibited OAT3 with an IC50 0,84 µM. IC50 value was lower than the worst expected concentrations of selumetinib at the systemic level (50*Cmax,u), i.e. 1,2 µM and 1,75 for selumetinib dose of 25 mg and 50 mg.

Selumetinib also inhibited *in vitro* MATE1, MATE-2K and OCT2 with an IC50 = 46,4 µM, 82,4 µM and 5,64 µM, respectively.

In silico

PBPK modelling was applied to estimate the effects of moderate CYP3A4 and CYP2C19 inhibitors as well as the effect of mild and moderate inducers of CYP3A4. The results are summarised in Figure 5. Co-administration of moderate inhibitors of CYP3A4 and CYP2C19 were estimated by PBPK modelling to increase the exposure of selumetinib 1.3 to 1.4-fold. The mild inducer dexamethasone and moderate inducer efavirenz were predicted not to affect the exposure to selumetinib and to decrease exposure by 38%, respectively.



The dots and error bars nearby are geometric mean of ratios for each inhibitor/inducer, and the horizontal segments are the 90% confidence interval of geometric mean. The observed values in itraconazole, fluconazole and rifampicin clinical DDI studies (Study D1532C00083 and D1532C00085). Grey area shows the 0.67- to 1.5-fold range.

AUC Area under the plasma concentration-time curve; CI Confidence interval; Cmax Maximum plasma concentration; DDI Drug-drug interaction.

Figure 5: Predicted and observed effects of CYP2C19 inhibitors, CYP3A4 inhibitors and CYP3A4 inducers on the exposure of selumetinib using PBPK modelling (report MS-02)

Qualification of the PBPK platform

Based on the data provided, the PBPK platform is considered qualified to evaluate the effect of CYP3A4 modulators on selumetinib exposure.

Sensitivity analysis

Sensitivity analyses were made with the protein binding fu, CYP3A4 and CYP2C19 Ki for inhibition by itraconazole and fluconazole, and IndC50 for induction by rifampicin as well as selumetinib f_m for CYP3A4 and CYP2C19.

In summary, as regards itraconazole Ki values, for both selumetinib predicted Cmax and AUC ratio changes were minor in the range of Ki tested. Similar results were observed with fluconazole Ki values tested. A sensitivity analysis was applied by changing CYP3A4 IndC50 from 0.032 to 3.2 µM. The Cmax ratio or AUC ratio increased rapidly as the IndC50 value increased for CYP3A4, indicating this is a sensitive parameter in the model.

A CYP3A4 fm of 25% provided a reasonable AUC ratio prediction for the itraconazole interaction (1.52 predicted versus 1.49 observed) and a CYP3A4 fm of 15% provided a reasonable Cmax ratio prediction for the itraconazole interaction. However, a fm of 25% for CYP3A4 was applied in the current PBPK to consider the "worst" case scenario. For CYP2C19 contribution, a fm of 15% could provide reasonable predictions for both AUC and Cmax ratio for the fluconazole interaction, therefore a fm of 15% was used in the model. The Applicant conducted additional sensitivity analysis on selected parameters subject to variability: f_u, Ki, IndC50 and f_m to support the robustness of the PBPK model.

Impact of time interval

The impact of timing intervals was also evaluated between administration of selumetinib and strong and moderate CYP3A4 and CYP2C19 inhibitors by using PBPK modelling. The simulations predicted AUC and C_{max} ratio of selumetinib administered simultaneously, or 4, 8 and 12 hours after itraconazole or fluconazole and data show similar results as those observed when drugs are given concomitantly.

Active metabolite and PBPK

The active selumetinib metabolite was shown to be about 3 to 5 times more potent than the parent compound and to contribute about 21% to 35% of the overall pharmacologic activity (see section 2.3.3). Additional simulations integrating selumetinib metabolite PK with or without itraconazole, fluconazole and rifampicine were conducted. The predicted C_{max} and AUC ratios of selumetinib metabolite were within 0.6 to 1.5-fold of the observed values.

Impact of a CYP3A4 and CYP2C9/2C19 inhibitor

A PBPK modeling and simulation was performed with voriconazole as both a CYP3A4 and CYP2C19 inhibitor. Results predicted an increase of selumetinib AUC ratio about 65% which is higher than the predicted and observed AUC ratio with itraconazole, about 52% and 49%, respectively.

Concomitant use of erythromycin (moderate CYP3A4 inhibitor) or fluoxetine (strong CYP2C19/CYP2D6 inhibitor) is predicted to increase selumetinib AUC by ~30-40% and C_{max} by ~20%.

Impact of combined UGT1A1 and CYP3A4 inhibition

PBPK simulations of the impact of a combined UGT1A1 and CYP3A4 inhibitor showed a predicted increase of selumetinib exposure about 63%, slightly higher the predicted increase with itraconazole, about 52%.

Impact of

In vivo

Based on *in vitro* data, two clinical interaction studies were conducted to assess the magnitude of the potential interactions with selumetinib:

- the effect of itraconazole, a strong CYP3A4 inhibitor, and fluconazole, a moderate CYP3A inhibitor and also a CYP2C9 and 2C19 inhibitor on selumetinib pharmacokinetics were investigated in study D1532C00083.

- the effect of rifampicin as a strong CYP inducer on selumetinib pharmacokinetics was investigated in study D1532C00085.

Table 9: Effect of itraconazole (200 mg bid), fluconazole (200 mg qd) and rifampicin (600 mg qd) on the pharmacokinetics of single dose selumetinib (studies 83 and 85)

			selumetinib		N-desmethyl selumetinib	
		Number of subjects	Ratio selumetinib+modifier/ selumetinib alone	90% CI	Ratio selumetinib+modifier/ selumetinib alone	90% CI
Itraconazole 200 mg BID	AUCt	24	1.48	1.39–1.58	0.89	0.82-0.96
	Cmax	24	1.18	1.04–1.35	0.79	0.67-0.85
Fluconazole 200 mg QD	AUCt	22	1.54	1.45–1.65	1.40	1.29-1.52
	Cmax	22	1.26	1.10–1.43	1.06	0.94-1.20
Rifampicin	AUCt	22	0.49	0.46–0.52	0.46	0.42-0.49

600mg QD	Cmax	22	0.74	0.66–0.83	0.82	0.71-0.94

The applicant explored the PK for 6 genetic variants UGT1A1*6, UGT1A1*26, ABCG2 421C>A, CYP2C19*2, CYP2C19*3 and CYP2C19*17 in studies D1532C00066, D1532C00083, and D1532C00086. A non-statistically significant higher exposure of selumetinib exposures in subjects with two alleles of ABCG2 421C>A was observed. No relationship with selumetinib exposure was observed for CYP2C19 genetic variants.

2.4.3. Pharmacodynamics

Mechanism of action

No mechanism of action studies has been submitted with this application.

Primary and Secondary pharmacology

For primary pharmacology data, please refer to section 2.3.2.

QTc prolongation

Study D1532C00071 was a Phase I, Double-blind Selumetinib [Hyd-Sulfate]), placebo-controlled, open-label (Moxifloxacin) positive-controlled, randomised, three-period crossover study to assess the effects of single oral dose of selumetinib (75 mg) on QTc interval compared to placebo, using AVELOX (Moxifloxacin) as a positive control, in healthy male volunteers aged 18 to 45 years old.

Following a single oral dose of selumetinib 75 mg, the highest upper bound of the 2-sided 90% CIs for ΔΔQTcF over the 24-hour post dose measurement interval was 2.5 msec on the primary analysis, which was lower than the protocol-specified 10 msec upper bound for concluding no effect.

Following a single oral dose of moxifloxacin 400 mg, the lower bound of the 2-sided 90% CI for mean ΔΔQTcF over the 1- to 4-hour time interval post dose was greater than 5 msec (ie.9.4 msec) on the primary analysis, thereby establishing assay sensitivity.

Mean differences for all ECG intervals were small for selumetinib treatment compared to placebo; differences ranged from -3.7 to 0.8 bpm for HR, -0.4 to 0.5 msec for QRS, and 0.1 to 5.3 msec for PR over the 0.5-hour to 24-hour post dose measurement period.

No volunteers on selumetinib or placebo treatment had QTcF or QTcB values >450 msec or changes from baseline >30 msec during the study. There were no HR events for selumetinib or placebo that met the predefined criterion of >100 bpm.

No PK/PD relationship was observed between selumetinib and N-desmethyl-selumetinib concentrations versus observed, change-from-baseline, and placebo-subtracted change-from-baseline QTcF and QTcB values.

PK/PD modelling

Two exposure-response (ER) analysis (efficacy and safety) using the predicted exposure metrics (AUCss, Cmaxss and Cminss) by the developed popPK model for both selumetinib and N desmethyl selumetinib were submitted.

ER-efficacy

Relationship between predicted PK exposure metrics and ORR was investigated, on two datasets (NCI dataset included Phase I and Phase II, ICR dataset included only Phase II). Using NCI central analysis, DoR (duration of response), PFS, best tumour size change and pain score from patient reported outcome were assessed vs. exposure of selumetinib and N-desmethyl metabolite.

For ORR using an exploratory analysis (boxplot), on the NCI dataset a slight trend of decreasing AUCss or Cmaxss appears to be associated to lower response. On the ICR dataset a similar trend is observed. Binomial logistic regression on AUCss of selumetinib versus response indicated no significant exposure-ORR relationship in the Phase I and Phase II efficacy data from SPRINT using the NCI central analysis while with the independent central review shows a minor trend towards higher exposure having higher ORR (p=0.0428) .

For PFS, DoR, tumour size change and pain score no clear relationship was identified for both compounds.

ER-safety

An exploratory analysis between the most common AE (13 categorical AE) and the predicted PK exposure metrics was performed. In addition, TTO (time to onset) and adverse events actions (no change, dose changed, withdrawn) were also explored. Overall no clear relationship was observed.

Dose rationale

Study D1532C0005 in adult patients with advanced malignancies where selumetinib capsules dose from 25 mg to 100 mg were administered, investigated the inhibition of phosphorylation of ERK considered as an indirect measure of MEK inhibition by selumetinib. A direct relationship between selumetinib plasma concentration and the inhibition of ERK phosphorylation was observed, with the highest inhibition occurring at the higher selumetinib plasma concentrations.

In SPRINT study, since no ERK phosphorylation activity was available, the plasma concentration of selumetinib and its active N-desmethyl metabolite were combined with a weighting applied for increase potency of the metabolite. The percent inhibition of pERK appears similar between the 20 mg/m² and 25 mg/m², 30 vs 33% respectively (data not shown). In addition such inhibition was linked to a combined exposure PK parameter (weighting sum of parent and 3 time metabolite).

The proposed recommended oral dose of selumetinib is 25 mg/m² of body surface area (BSA), taken twice daily (BID). Dosing is individualized based on BSA (mg/ m²) and rounded to the nearest achievable 5 mg or 10 mg (up to a maximal single dose of 50 mg) as presented in Table 13.

2.4.4. Discussion on clinical pharmacology

Throughout the clinical development, different bioanalytical methods were used to quantify selumetinib and its active metabolite N-desmethyl selumetinib in human plasma with K2EDTA as anticoagulant. Despite the absence of cross-validation data, there is no indication that the use of different bioanalytical methods resulted in different PK results based on popPK analysis.

The PK of selumetinib in paediatric patients aged 3 to 18 years old with NF1 and inoperable PN have been adequately characterised following single and multiple dosing based on BSA in the dedicated pivotal phase 1/ 2 study 057 (SPRINT). To identify a suitable dose, phase I portion of SPRINT study evaluated 3 doses of selumetinib, 20, 25 and 30 mg/m² (n= 9, 4 and 5, respectively), then 25 mg/m² level was selected as the recommended dose for the extension Phase II portion (n= 45) (see also section 2.5.1).

Koselugo is for oral use. In view of the effect of food on the PK of selumetinib, it should be taken on an empty stomach with no food or drink other than water 2 hours prior to dosing and 1 hour after dosing. The capsules should be swallowed whole with water. The capsules should not be chewed, dissolved, or

opened, because this could impair drug release and affect the absorption of selumetinib (see sections 4.2, 4.5 and 5.2).

If a dose of Koselugo is missed, it should only be taken if it is more than 6 hours until the next scheduled dose.

A high frequency of gastrointestinal adverse events has been observed in paediatric patients. The applicant is recommended to provide the results from study D1346C00015 evaluating the effect of a low-fat meal on PK and tolerability in adolescents. The first CSR report is to be expected 3Q 2022. Since an age-appropriate formulation showing no food effect on AUC and smaller decrease in Cmax compared with capsules, is under development, the applicant may consider using this formulation for this study. In addition, the applicant is recommended to evaluate PK and tolerability of the age-appropriate formulation in paediatric patients 1-7 years of age (study D1346C00004). The expected timing of study report is Q3 2023.

A pooled Pop PK model for selumetinib and its N-desmethyl metabolite was developed based on plasma concentrations of selumetinib and N-desmethyl selumetinib issued from 10 Phase I studies in healthy subjects, 2 Phase I studies in adult patients with advanced solid malignancies and the SPRINT study in children with NF1. Overall, the developed Pop PK model could be considered adequate to describe the PK characteristics of selumetinib and appropriate for use in predictions of selumetinib systemic exposures. The PK parameters in adult healthy subjects and adult patients with advanced solid malignancies, are similar to those in paediatric patients (3 to ≤ 18 years old) with NF1.

BSA was identified as a significant covariate impacting PK parameters of selumetinib (impact of CL >30% in the extremes of the observed BSA distribution).

The recommended dose of Koselugo is 25 mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours). Dosing is individualised based on BSA (mg/m^2) and rounded to the nearest achievable 5 mg or 10 mg dose (up to a maximum single dose of 50 mg). Different strengths of Koselugo capsules can be combined to attain the desired dose (Table 13). Simulations have shown that the recommended 25 mg/m² BSA-based dosing provide similar systemic exposure of selumetinib across BSA bands.

Renal impairment is expected to have no meaningful influence on the exposure of selumetinib. As exposure in end stage renal disease (ESRD) subjects was similar to those with normal renal function, investigations in mild, moderate and severe renally impaired subjects were not performed. No dose adjustment is recommended in patients with mild, moderate, severe renal impairment or those with ESRD (see sections 4.2 and 5.2 of the SmPC).

Based on clinical trials, no dose adjustment is recommended in patients with mild hepatic impairment. The starting dose should be reduced in patients with moderate hepatic impairment to 20 mg/m2 BSA, twice daily. Koselugo is contraindicated for use in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2 of the SmPC).

Following a single-dose, selumetinib exposure appears to be higher in Japanese, non-Japanese-Asian and Indian healthy adult subjects compared to Western adult subjects, however, there is considerable overlap with Western subjects when corrected for body weight or BSA. No specific adjustment to the starting dose is recommended for paediatric Asian patients, however these patients, should be closely monitored for adverse events (see sections 4.2 and 5.2 of the SmPC).

In vitro, selumetinib is not an inhibitor of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP2E1.

In vitro, selumetinib is not an inducer of CYP1A2 and CYP2B6. Selumetinib is an inducer of CYP3A4 in vitro, this is however not expected to be clinically relevant.

In vitro, selumetinib inhibits UGT1A3, UGT1A4, UGT1A6 and UGT1A9 however these effects are not expected to be clinically relevant.

DDI studies show that co-administration with medicinal products that are strong inhibitors of CYP3A4 (e.g., clarithromycin, grapefruit juice, oral ketoconazole) or CYP2C19 (e.g., ticlopidine) should be avoided. Co administration with medicinal products that are moderate inhibitors of CYP3A4 (e.g., erythromycin and fluconazole) and CYP2C19 (e.g., omeprazole) should be avoided. If co-administration is unavoidable, patients should be carefully monitored for adverse events and the selumetinib dose should be reduced. If a patient is currently taking 25 mg/m^2 twice daily, the dose should be reduced to 20 mg/m^2 twice daily. If a patient is currently taking 20 mg/m^2 twice daily, the dose should be reduced to 15 mg/m^2 twice daily.

Table 10: Recommended dosage to achieve 20 mg/m^2 or 15 mg/m^2 twice daily dose level

Body Surface Area	20 mg/m^2 twice daily (mg/dose)		15 mg/m^2 twice daily (mg/dose)	
	Morning	Evening	Morning	Evening
0.55 – 0.69 m^2	10	10	10 mg once a day	
0.70 – 0.89 m^2	20	10	10	10
0.90 – 1.09 m^2	20	20	20	10
1.10 – 1.29 m^2	25	25	25	10
1.30 – 1.49 m^2	30	25	25	20
1.50 – 1.69 m^2	35	30	25	25
1.70 – 1.89 m^2	35	35	30	25
≥ 1.90 m^2	40	40	30	30

In addition, concomitant use of strong CYP3A4 inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) or moderate CYP3A4 inducers with Koselugo should be avoided.

In vitro studies suggest that selumetinib does not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, MATE1 and MATE2K at the recommended paediatric dose*. In vitro,* selumetinib is an inhibitor of OAT3. The potential for a clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 (e.g., methotrexate and furosemide) cannot be excluded (see sections 4.2, 4.5 and 5.2 of the SmPC).

More than 30% of the paediatric patients used concomitant medication with histamine H2-antagonists, proton pump inhibitors or antacids. Selumetinib capsules do not exhibit pH dependent dissolution. Koselugo can be used concomitantly with gastric pH modifying agents (i.e. H2 receptor antagonists and proton pump inhibitors) without any restrictions, except for omeprazole which is a CYP2C19 inhibitor. However, monitoring of these combinations through routine pharmacovigilance is recommended.

The commercial product contains Vitamin E polyethylene glycol succinate (TPGS) as excipient. TPGS has the potential to increase the bioavailability of orally administered drug presumably by inhibition of efflux transporters (Guo et al. 2013, Chang et al. 1996, Bogman et al., 2005). It cannot be excluded that it may cause clinically relevant drug interactions with substrates of P-gp (e.g. digoxin or fexofenadine).

The effect of selumetinib on the exposure of oral contraceptives has not been evaluated. It cannot be excluded that selumetinib may reduce the effectiveness of oral contraceptives, therefore women using hormonal contraceptives should be recommended to add a barrier method (see sections 4.5 and 4.6 of the SmPC).

2.4.5. Conclusions on clinical pharmacology

An extensive clinical pharmacology program, including formal PK studies including mass balance, food effect, hepatic and renal impairment, as well as population PK analysis (in adults and paediatric patients) and DDI assessment has been provided. Overall, the PKs of selumetinib has been sufficiently characterised in healthy subjects, adult patients with solid tumours and in the target population of paediatric patients aged 3 to 18 years old with NF-1 and inoperable PN (pivotal phase 1 and 2 SPRINT study). The PK of selumetinib appears to be similar in adult and paediatric patients. The proposed BSA-based dosing regimen of selumetinib 25 mg/m² BID in children patients is supported.

Besides, the applicant is recommended to evaluate PK and tolerability of a low-fat meal in adolescents (study D1346C00015) and to evaluate PK and tolerability of the age-appropriate formulation in paediatric patients 1-7 years of age (study D1346C00004).

2.5. Clinical efficacy

2.5.1. Dose response study

Methods

- *Study design*

The dose response study is a Cancer Therapy Evaluation Program (CTEP)-sponsored Phase I, open-label, single-arm, multiple-dose, dose-escalation, multi-centre study of selumetinib in paediatric patients with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibroma (PN).

Inoperable PN was defined as PN that cannot be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN.

Table 11: Key design features of SPRINT Phase I

	D1532C00057 SPRINT Phase I
Population	Patients aged ≥3 and ≤18 years with NF1 and inoperable PN[a], who: - had at least 1 measurable PN, defined as a PN of at least 3 cm measured in one dimension. Patients who had undergone surgery for resection of a PN were eligible, provided the PN had been incompletely resected and was measurable. - had the ability to swallow whole capsules (since capsules cannot be crushed or broken). - had not received prior treatment with selumetinib or another specific MEK1/2 inhibitor.
Selumetinib dose	20, 25 and 30 mg/m^{2}[b]

	D1532C00057 SPRINT Phase I
Duration of study and study treatment	Patients continued in the study until they met at least 1 of the off-study criteria. In order to limit the potential for exposure to selumetinib in the absence of clinical benefit, the following caveats were applied: - For patients with documented disease progression within approximately 1.5 years prior to study entry (i.e., ≥20% increase in PN volume or ≥13% increase in the product of longest 2 perpendicular diameters or ≥6% increase in longest diameter), there was no limit to the duration of treatment as long as the patient met the requirements for further treatment and at the discretion of the institutional principal investigator. - For patients with no documented history of disease progression within the 1.5 years prior to study entry, treatment duration was limited to 2 years if no imaging response (response=volume decreased by ≥20%) was observed. Patients who were removed from treatment after 2 years of therapy for reasons other than toxicity or progression, and who had stable disease, continued to be monitored with volumetric MRI analysis every 4 to 6 months. If the target PN demonstrated some growth (volume increase ≥15%) within approximately 2 years of stopping selumetinib, treatment with selumetinib could be re-started (re-treatment) with the goal to stop further PN growth. Patients were to be re-consented to the study and were required to meet all eligibility criteria, with the exception of prior treatment with selumetinib or another specific MEK 1/2 inhibitor, prior to selumetinib re treatment. Selumetinib re-treatment could continue as long as the target PN remained stable or responsive.
Primary endpoints	MTD and RP2D; Day 1 and steady state PK of selumetinib.
Key secondary efficacy endpoint	Percentage PN volume change, calculated from measurements taken using volumetric MRI analysis[c]
Key exploratory efficacy endpoints	ORR, DoR, and TTR based on evaluation of target PN only, using volumetric MRI analysis[d]
PN response assessment schedule	Pre-study; prior to Cycles 6 and 11, and every 6 cycles thereafter; and at the end of selumetinib treatment, if possible.
Analysis sets	- The DLT Analysis Set included all patients who either completed the DLT evaluation period with sufficient dosing or who received 1 or more doses and experienced a DLT during that period. - The Safety Analysis Set included all patients who received at least 1 dose of selumetinib. - The PK Analysis Set included all patients who received at least 1 dose of selumetinib and had at least 1 post-dose sample taken for PK analysis. - The Full Analysis Set included all patients who received at least 1 dose of selumetinib (Note: this was the same as the Safety Analysis Set in this study).
Geographical location	4 sites in the United States
Planned enrolment	At least 21 patients

a Defined as PN that cannot be surgically completely removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN.

b In SPRINT Phase I, selumetinib was administered orally BID (approximately every 12 hours) on a continuous schedule; the dose was capped at 50 mg when BSA was ≥1.9 m2. A cycle of therapy was considered to be 28 days with no rest periods in between cycles.

c Provides supporting evidence to the analysis of volumetric PN growth in SPRINT Phase II Stratum 1.

d Provides supporting evidence to the analysis of ORR, DoR and TTR in SPRINT Phase II Stratum 1.

Note that ICR analysis of the volumetric MRI images was not performed in SPRINT Phase I.

BID Twice daily; BSA Body surface area; DLT Dose-limiting toxicity; DoR Duration of response; ICR Independent central review; MTD Maximum tolerated dose; ORR Objective response rate; PN Plexiform neurofibroma(s); PK Pharmacokinetics; RP2D Recommended Phase II dose; TTR Time to response.

- *Objectives*

The primary objective of SPRINT Phase I was to determine the safety and tolerability, the recommended Phase II dose (RP2D), and plasma PK at baseline and steady state, of selumetinib in children and

adolescents with NF1 and inoperable PN. The secondary objectives included effect on PN growth rate and the exploratory objectives included ORR, DoR and TTR.

Results

Patient disposition

In total, 24 patients were enrolled in SPRINT Phase I. Twelve patients received selumetinib 20 mg/m^2 BID, 6 patients received selumetinib 25 mg/m^2 BID and 6 patients received selumetinib 30 mg/m^2 BID. In total, 45.8% of patients discontinued treatment. AEs and 'Other' were the most common reason for treatment discontinuation. Within the 'Other' category, 2 patients discontinued because it was 'deemed in the patient's best interest' as assessed by the investigator and 1 patient discontinued based on 'tumour becoming resistant'. At DCO, 54.2% of patients were continuing to receive selumetinib.

There were 17 screen failures in SPRINT Phase II Stratum 1, the reasons being: for 9 patients 'compliance with study criteria' (e.g., tumour not measurable, no PN-related morbidities, metal work in situ, compliance issues); for 4 patients 'patient/ family decision'; for 4 patients 'medical reasons' (e.g., hypertension, surgery, increased intra ocular pressure); and for a single patient 'no information given'.

Demographic and disease characteristics

Demographic and other patient characteristics at baseline for SPRINT Phase I are summarised in Table 17.

The median age at enrolment was 10.9 years (range: 3.0 to 18.5 years); 54.2% of patients were male and 75.0% of patients were White. The median time from diagnosis of NF1 and PN to start of selumetinib treatment was 8.75 years (range 1.42-17.0 years) and 8.28 years (range 0.79-17.0 years), respectively.

At baseline the median target PN volume was 1204.50 mL (range: 29.4 to 8744.0 mL). Nineteen patients (79.2%) had received prior medical therapy for PN and/or another NF1-related tumour. The three most common medical therapies (>20% of patients at the Anatomical Therapeutic Chemical [ATC] level) received by these patients were interferons (including peginterferon), selective immunosuppressants (sirolimus) and protein kinase inhibitors (imatinib).

Table 12: Patient characteristics: SPRINT Phase I (FAS)

		SPRINT Phase I Selumetinib Total (N=24)
Age, years[a]	Mean (SD)	10.9 (4.68)
	Median (min max)	10.9 (3.0-18.5)
Sex, n (%)	Male	13 (54.2)
	Female	11 (45.8)
Race, n (%)	White	18 (75.0)
	Black or African American	2 (8.3)
	Asian	2 (8.3)
	Unknown/other	2 (8.3)
Height, cm	n	24
	Mean (SD)	136.31 (24.158)
	Median (min-max)	135.60 (98.5-173.6)
Weight, kg	n	24
	Mean (SD)	37.85 (19.958)
	Median (min-max)	30.34 (16.8-88.7)

		SPRINT Phase I Selumetinib Total (N=24)
Lansky performance status score[c]	n	20
	Mean (SD)	89.5 (10.50)
	Median (min-max)	90 (70-100)
Karnofsky performance status score[c]	N	4
	Mean (SD)	87.5 (5.00)
	Median (min-max)	90 (80-90)
Target PN volume, mL	Median (min-max)	1204.50 (29.4-8744.0)
Prior PN-directed medical treatments[d]	Yes	19 (79.2) [e]
	No	5 (20.8)

a Age at informed consent.

b Lansky performance status was assessed in patients who were 16 years of age or younger and Karnofsky performance status was assessed in patients who were older than 16 years of age. Both the Lansky performance status and the Karnofsky performance status scores range from 10 to 100, with higher scores indicating better functioning.

Note: Patients in SPRINT Phase I received either 20 mg/m^2 BID (n=12), 25 mg/m^2 BID (n=6) or 30 mg/m^2 BID (n=6) selumetinib.

ATC Anatomical Therapeutic Chemical; BID Twice daily; CSR Clinical Study Report; DCO Data cut-off; FAS Full Analysis Set; MRI Magnetic resonance imaging; NA Not available; NF1 Neurofibromatosis type 1; NH Natural History; PN Plexiform neurofibroma(s); SD Standard deviation.

The starting dose level was 20 mg/m²/dose BID (approximately 50% of the adult maximum tolerated dose [MTD]). This was to be followed by up to 3 dose escalations, with the highest dose level exceeding the adult MTD by 1 dose level.

A contemporary study conducted by the Pediatric Brain Tumor Consortium (Banerjee et al 2017) determined, the MTD of paediatric patients with low-grade glioma as selumetinib 25 mg/m² BID and this additional dose level was added to the dose schema per protocol amendment.

As a secondary objective, automated volumetric MRI analysis was used to monitor PN growth rate. PN growth rate was evaluated by a single National Cancer Institute- Paediatric Branch Oncology (NCI POB) reviewer who is a leading expert in the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) tumour imaging working group.

In total, 24 paediatric patients were enrolled and treated with selumetinib at 4 sites in the US. At DCO (Data cut-off), 16 (66.7%) patients remained within the study; of these 13 (54.2%) patients remained on selumetinib. In total, 11 patients discontinued selumetinib; the reasons were: AE (3 patients), disease progression (2 patients), patient not willing to continue (2 patients), treatment period completed (1 patient) and other (3 patients). Eight patients discontinued the study; the most common reason was voluntary discontinuation by patient (4 patients).

Table 13: Dose-limiting toxicity events in Cycles 1 to 3 (DLT Analysis Set, SPRINT Phase I)

Selumetinib assigned Cycle 1 dose	N	Number of evaluable patients with a DLT	AE MedDRA PT/CTCAE grade/cycle number
20 mg/m² BID	12	2	urticaria/Grade 3/1 vulval cellulitis/Grade 3/1
25 mg/m² BID	6	1	pruritus/Grade 2/2 rash maculo-papular/Grade 3/2
30 mg/m² BID	6	2	blood creatine phosphokinase increased/Grade 3/2 ejection fraction decreased/Grade 3/5[a]

[a] Late DLT reported per Protocol Amendment G (Section 5.1).

AE Adverse event; BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events (Version 4.0); DLT Dose-limiting toxicity; MedDRA Medical Dictionary for Regulatory Activities (Version 21.0); PT Preferred term.

The starting dose level was 20 mg/m² BID, which was tolerated (no patients had a DLT (Dose-limiting toxicity)). The dose was escalated to 30 mg/m² BID, which was not tolerated (2/6 patients had DLTs). Based on the dose-limiting toxicity Analysis Set, the recommended Phase II dose was 25 mg/m² BID.

Efficacy Outcomes and estimation

Efficacy of selumetinib, as assessed by target PN volume measurements, was a secondary objective for this study.

Table 14: Confirmed objective response rate (SPRINT Phase I)

	Selumetinib 20 mg/m² BID (N=12)	Selumetinib 25 mg/m² BID (N=6)	Selumetinib 30 mg/m² BID (N=6)	Total (N=24)
Number (%) of patients with a response[a]	8 (66.7)	5 (83.3)	3 (50.0)	16 (66.7)
95% CI[b]	34.9, 90.1	35.9, 99.6	11.8, 88.2	44.7, 84.4

[a] Response was defined as PN decrease ≥20% compared with baseline for ≥4 weeks.

[b] The CIs were calculated using Clopper-Pearson exact method for binomial proportions.

ORR was defined as the number (%) of patients with CR or cPR and was based on patients who received at least 1 dose of selumetinib.

BID Twice daily; CI Confidence interval; cPR Confirmed partial response; CR Complete response; ORR Objective response rate; PN Plexiform neurofibroma(s).

The objective response rate (ORR) analyses was based on the Full Analysis Set population. Responses were reported at all dose levels. Of the 24 patients treated:

- 16 (66.7%; 95% CI: 44.7, 84.4) patients had a confirmed partial response (cPR) (target PN volume decrease ≥20% from baseline for ≥4 weeks),

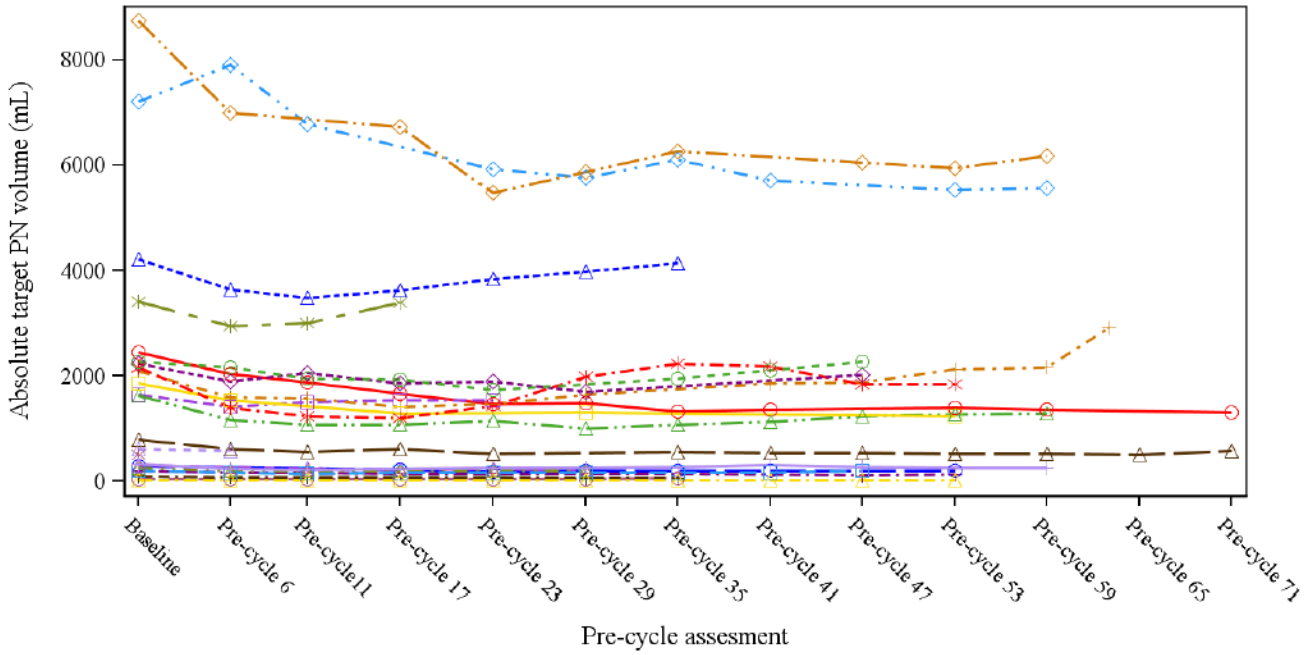
- 2 (8.3%) patients had an unconfirmed PR,

- 5 (20.8%) patients had stable disease.

No patient (0%) had a CR; no patient (0%) had progression; and 1 patient (4.2%) was not evaluable (this patient did not have any response derivations, primarily due to out-of-window visits).

Target PN volume changes over time

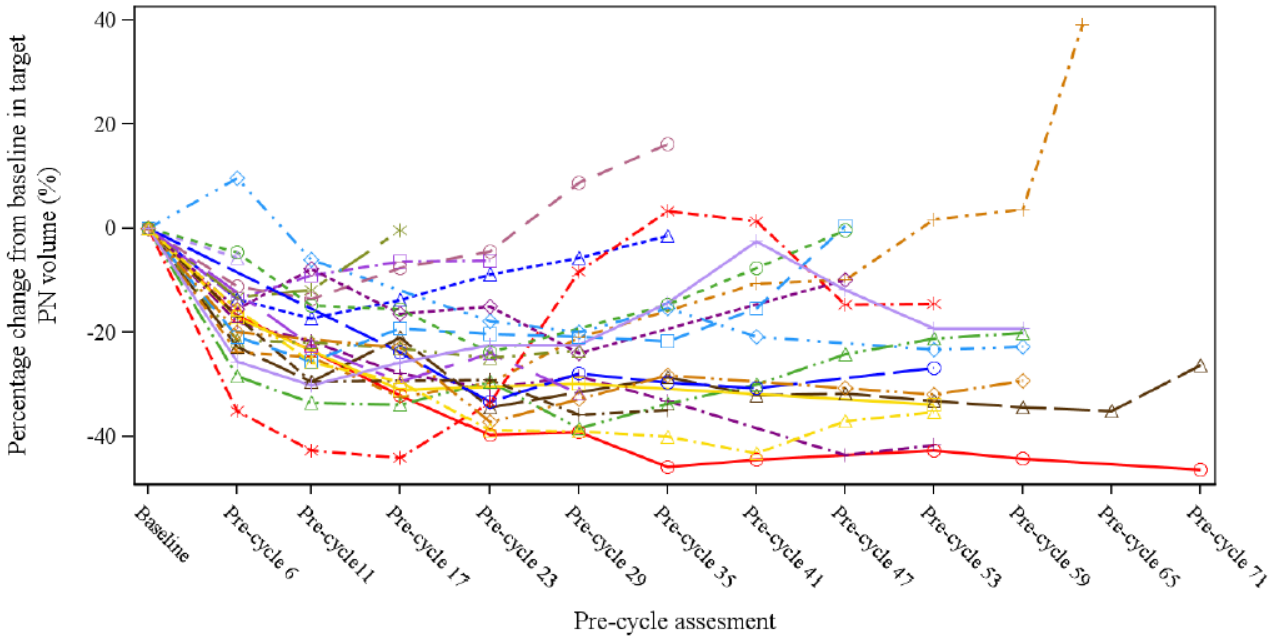
The spaghetti plot in Figure 6 shows each patient's PN volume over time.



One patient had a progression at Pre-cycle 63. Another patient had a noted progression based on a partial tumour volume measurement at Pre-cycle 52.

Figure 6: Target PN volume, individual patient data over time: SPRINT Phase I (FAS)

The spider plot in Figure 7 shows each patient's percentage change in target PN volume over time.



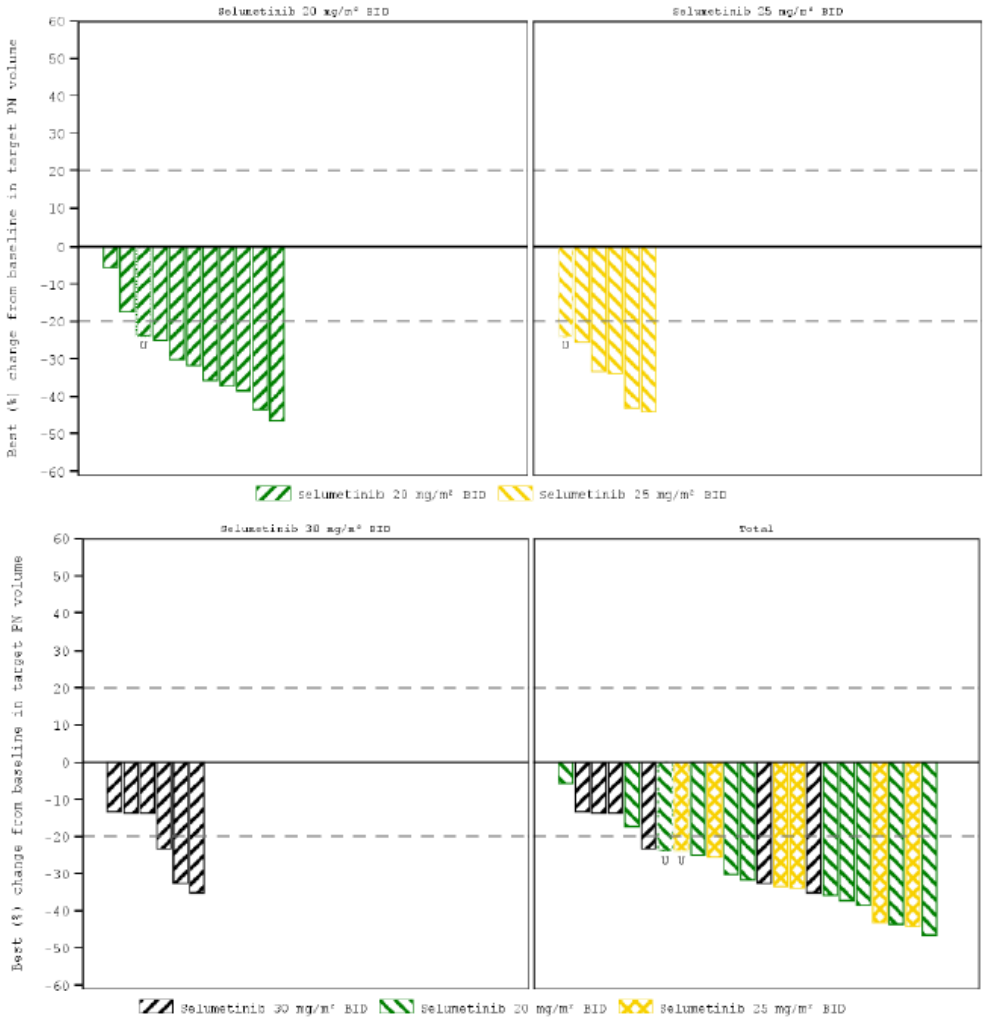
One patient had a progression at Pre-cycle 63. Another patient had a noted progression based on a partial tumour volume measurement at Pre-cycle 52.

Figure 7: Percentage change in target PN volume, individual patient data over time: SPRINT Phase I (FAS)

Best percentage change from baseline

Twenty-three of the 24 patients were included in the summary of best percentage change from baseline. Data for 1 patient (who was treated with selumetinib 20 mg/m^2) was not included, primarily due to out-of-window scans. All of the 23 included patients had a reduction from baseline in target PN volume as

BOR and the median best percent change from baseline in target PN volume was -31.72% (range -46.5, -5.7).



Best percentage change in target PN volume was the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction.
BID Twice daily; PN Plexiform neurofibroma(s).
Figure 8: SPRINT Phase I (supportive data): Waterfall plot of best percentage change from baseline in target PN volume (FAS)

DoR

At DCO, median DoR from onset of response was not reached, as only 1 of the 16 patients with a confirmed response had subsequently progressed. All 16 responders had been followed up for at least 16 months from the onset of response (range: 18 to 65 cycles), and the number (percentage) of patients remaining in response after 16, 22 and 28 cycles was 16 (100%), 14 (87.5%), and 12 (75.0%), respectively.

In the post-hoc supplementary analysis using all available scans, two responders eventually progressed at 33.1 and 46.3 months after response onset, respectively. For this analysis, median DoR was not reached and the number (percentage) of patients remaining in response after 16, 22 and 24 months was 17 (100%), 16 (94.1%), and 14 (82.4%), respectively.

TTR

The median TTR for the 16 responders was 7.5 cycles (95% CI: 5.0, 10.0). At the first assessment (at 5 cycles) 8 of these (50.0%) had their response, and by 10 cycles this number had increased to 13 (81.3%).

PFS

At DCO, median PFS was not reached (with a median follow-up for PFS of 49.0 cycles), as only 2/24 patients (8.3%) had progressed (none had died).

In the post-hoc supplementary analysis using all available scans, 4/24 patients (16.7%) had progressed, i.e., 2 more than in the main PFS analysis. For this analysis, median PFS was not reached.

2.5.2. Main study

A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK) 1 Inhibitor Selumetinib (AZD6244; HYD Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN) (SPRINT Phase II Stratum 1)

SPRINT Phase II is an ongoing CTEP-sponsored, open-label, single-arm, multi-centre study of selumetinib in children with NF1 and inoperable PN, with PN-related morbidity at enrolment, and was conducted by the NCI POB (National Cancer Institute- Paediatric Branch Oncology).

Methods

Study Participants

Patients were enrolled on 1 of 2 strata based on whether they already had PN-related morbidity (Stratum 1) or had no significant clinical morbidity (Stratum 2) but the potential for significant clinical PN-related morbidity at the time of enrolment (see inclusion criteria). Stratum 2 data were not included in this application.

The main criteria for **inclusion** in SPRINT Phase II Stratum 1, were:

- **Age**: ≥2 and ≤18 years at the time of enrolment. Body surface area ≥0.55 m² and ability to swallow whole capsules (assessed at screening using an empty capsule shell). The age criteria were chosen because early childhood and puberty are considered to be the greatest risk for disease progression, and selumetinib may provide the most benefit to this young group of patients.
- **Diagnosis**: patients with NF1 (per NIH Consensus Conference criteria) and inoperable PN, defined as PN that could not be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN.

The PN had to cause significant morbidity, such as (but not limited to) head and neck PN that could have compromised the airway or great vessels, paraspinal PN that could have caused myelopathy, brachial or lumbar plexus PN that could have caused nerve compression and loss of function, PN that could have resulted in major deformity (e.g. orbital PN) or were significantly disfiguring, PN of the extremity that could have caused limb hypertrophy or loss of function, and painful PN.

- **Measurable disease**: patients must have had at least 1 measurable PN, defined as a PN of at least 3 cm measured in 1 dimension. Patients who had undergone surgery for resection of a PN were eligible, provided the PN had been incompletely resected and was measurable. Measurability and suitability for volumetric MRI analysis of the target PN had to be confirmed with the NCI POB prior

to enrolment. The target PN was defined as the clinically most relevant PN, which had to be amenable to volumetric MRI analysis.

- **Performance status**: patients >16 years of age must have had a Karnofsky performance level of ≥70%, and patients ≤16 years old must have had a Lansky performance of ≥70%.
- **Normal/adequate** haematologic, hepatic, renal, and cardiac function, and adequate blood pressure.
- **Prior therapy:** patients with NF1 were only eligible if complete PN resection was not considered to be feasible without substantial risk or morbidity.

  Since there is no standard effective chemotherapy for patients with NF1 and PN, patients could have been treated on this study without having received prior medical therapy directed at their PN.

  - Since selumetinib is not expected to cause substantial myelosuppression, there was no limit to the number of prior myelosuppressive regimens for PN, or other tumour manifestations associated with NF1, such as optic glioma.
  - Patients who had received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorafenib, imatinib or other targeted therapies were eligible for enrolment. At least 4 weeks must have elapsed since receiving medical therapy directed at the PN. Patients who received prior medical therapy for their PN must have recovered from the acute toxic effects of all prior therapy to ≤Grade 1 Common Terminology Criteria for Adverse Events (CTCAE) v4 before entering this study.
  - Growth factors that support platelet or white cell number or function must not have been administered within the 7 days prior to enrolment.
  - At least 6 weeks must have elapsed prior to enrolment since the patient received any prior radiation therapy.
  - At least 4 weeks must have elapsed since any surgeries, with evidence of good wound healing.

The main **exclusion** criteria for in SPRINT Phase II Stratum 1, were:

- Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumour, immunotherapy or biologic therapy.
- Any evidence of severe or uncontrolled systemic disease, active infection, active bleeding diatheses, or renal transplant, including any patient known to have hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) were to be excluded. Patients with HIV who had adequate CD4 count, not requiring antiretroviral medication, could be enrolled.
- Inability to swallow capsules, since capsules cannot be crushed or broken.
- Evidence of an optic glioma, malignant glioma, MPNST, or other cancer requiring treatment with chemotherapy or radiation therapy.
- Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must have been stopped prior to initiation of therapy.
- Ophthalmologic conditions: current or past history of central serous retinopathy, current or past history of retinal vein occlusion, known intraocular pressure (IOP) >21 mmHg (or upper limit of normal [ULN] adjusted by age) or uncontrolled glaucoma (irrespective of IOP). Patients with any other significant abnormality on ophthalmic examination were to be discussed with the Study Chair for potential eligibility. Ophthalmological findings secondary to long-standing optic pathway

glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-temporal PN (such as visual loss, strabismus) were not considered a significant abnormality for the purposes of the study.

Treatments

Selumetinib was supplied as 10 mg and 25 mg capsules. Selumetinib was administered orally twice daily (approximately every 12 hours) continuously for 28-day cycles with no rest periods between cycles.

Patients were instructed to take the dose of selumetinib on an **empty stomach** (no food or drink other than water for 2 hours before and 1hour after dosing) with water only. The capsules were not to be crushed or broken and were to be swallowed whole.

Dosing

Dosing was performed based on BSA, and doses were rounded to the nearest 5 to 10 mg using a dosing nomogram. Selumetinib dosing was capped at 50 mg when BSA was ≥1.9 m². At follow-up evaluations during re-staging visits, selumetinib was adjusted for changes in BSA according to the dosing nomogram depicted in Table 20 below.

Table 15: SPRINT Phase II Stratum 1 dosing nomogram of selumetinib 25 mg/m² twice daily

Body Surface Area (BSA)	Dose in mg (twice daily)
0.55 – 0.59 m^2	10
0.60 – 0.89 m^2	20
0.90 – 1.09 m^2	25
1.10 – 1.29 m^2	30
1.30 – 1.49 m^2	35
1.50 – 1.69 m^2	40
1.70 – 1.89 m^2	45
≥ 1.90 m^2	50

If the patient experienced a toxicity requiring dose modification, selumetinib was to be withheld. If the toxicity resolved to meet study parameters or CTCAE v4.0 ≤Grade 1 within 21 days of drug interruption, the patient could resume selumetinib at a dose reduced by 25% to 33%.

If toxicity recurred in any patient who had resumed treatment at the reduced dose, the dose could have been reduced a second time using the same criteria, with the exception of cardiotoxicity, for which only 1 dose reduction was allowed.

Table 16: First selumetinib dose reduction

Selumetinib current dose (mg/dose BID)	Selumetinib first dose reduction (mg/dose)	Percent decrease (approximately) in selumetinib dose (%)
50	35 BID	30
45	35 AM and 30 PM	28
40	30 BID	25
35	25 BID	27
30	25 AM and 20 PM	25
25	25 AM and 10 PM	30
20	20 AM and 10 PM	25
10	10 QD even day 20 QD odd day	25

BID Twice daily; QD once daily.

Doses reduced for toxicity were in general not to be re-escalated, even if there was minimal or no toxicity with the reduced dose, with the following exception: the dose may have been increased to account for an increase in BSA at the time of on-study evaluations.

If toxicity recurred in any patient who had resumed treatment at the reduced dose, the dose could have been reduced a second time (i.e. a second selumetinib dose reduction; see Table 22) using the same

criteria, with the exception of cardiotoxicity, for which only 1 dose reduction was allowed. The criteria for toxicities other than cardiotoxicity were: the toxicity resolved to meet study parameters within 21 days of selumetinib discontinuation (unless receiving clear clinical benefit, as defined below under treatment duration), the dose was reduced 25% to 33%, could not have been re-escalated, and doses held were not made up.

Table 17: Second selumetinib dose reduction

Current selumetinib dose after dose reduction 1 (mg/dose)	Selumetinib second dose reduction (mg/dose)	Percent decrease (approximately) in selumetinib dose (%)
35 BID	25 BID	27
35 AM and 30 PM	25 AM and 20 PM	31
30 BID	25 AM and 20 PM	25
25 BID	25 AM and 10 PM	30
25 AM and 20 PM	20 AM and 10 PM	33
25 AM and 10 PM	25 AM and None PM	29
20 AM and 10 PM	10 AM and 10 PM	33
10 QD even day 20 QD odd day	10 QD even day 10 QD odd day	33

BID Twice daily; QD once daily.

If toxicity recurred after 2 dose reductions, the patient was removed permanently from selumetinib.

Treatment duration:

Patients continued in the study until they met at least 1 of the off-study criteria. In order to limit the potential for exposure to selumetinib in the absence of clinical benefit, the following caveats were applied:

- For **patients with** documented **disease progression** within approximately 1.5 years prior to study entry, defined as ≥20% increase in size of PN by volumetric MRI analysis (or ≥13% increase in the product of the longest 2 perpendicular diameters, or ≥6% increase in the longest diameter), there was to be **no limit to the duration** of treatment as long as the patient met the protocol-defined requirements for further treatment.

- For **patients with no** documented history of **disease progression** within the 1.5 years prior to trial entry, the duration of the study **was limited to 2 years if no** imaging **response** (i.e. response=volume decreased by ≥20%) **was observed**.

- **Re-treatment**: Patients who were removed from treatment after 2 years of therapy for reasons other than toxicity or progression, and who had stable disease, were continued to be monitored with volumetric MRI analysis every 4 to 6 months. If the PN demonstrated some growth (volume increase ≥15%) within approximately 2 years of stopping selumetinib, treatment with selumetinib could be re-started with the goal to stop further PN growth. Patients were to be re-consented on the study and meet all eligibility criteria, with the exception of prior treatment with selumetinib or another specific MEK 1/2 inhibitor prior to re-starting therapy. In these patients, treatment could continue as long as the PN remained stable or responsive (<20% increase in the PN volume).

- **For patients who showed** imaging **response the treatment duration was not to be limited**, unless the patient experienced subsequent disease progression or met other off-treatment criteria.

In all cases, treatment may have been discontinued earlier at the discretion of the institutional principal investigator if this was felt to be in the best interest of the patient.

Objectives

The primary objective was to evaluate confirmed partial and complete response rate of selumetinib using volumetric MRI analysis in children and young adults with NF1 and inoperable PN with PN-related morbidity at time of enrolment.

Secondary objectives included:

- Efficacy: Duration of response (DoR), time to progression (TTP), time to tumour response (TTR) and progression free survival (PFS).
- Clinical outcome measures related to the target PN: effect on pain, functional outcomes (motor dysfunction, airway dysfunction, visual dysfunction and bowel/bladder dysfunction as assigned at baseline), disfigurement.
- Health-related quality of life (QoL).
- Safety: Long-term tolerability and safety, and PK.

Outcomes/endpoints

Primary endpoint

The primary outcome variable pre-specified in the protocol was objective response rate (ORR), defined as the percentage of patients with a complete response (CR) or confirmed partial response (PR is target PN volume decrease from baseline ≥20%, confirmed when documented by subsequent volumetric MRI within 3 to 6 months):

- CR: Disappearance of the target PN
- PR: Decrease in the volume of the target PN by 20% or more compared with the baseline. The PR is considered unconfirmed at the first detection, confirmed when observed again within 3 to 6 months.
- Stable disease: Insufficient volume change from baseline to qualify for either PR or progressive disease.
- Progressive disease: Increase in the volume of the target PN by 20% or more compared with baseline or the time of best response after documenting a PR. The appearance of new PN (with the exception of new discrete subcutaneous neurofibromas) or unequivocal progression of existing clinically relevant non-target PN was also to be considered progressive disease.

The target PN was selected by the assessing investigator as the most clinically relevant PN, amenable to volumetric MRI analysis, to follow during the study.

Tumour response was evaluated at re-staging visits prior to Cycles 5, 9, 13, 17, 21, 25, and then after every 6 cycles until permanent discontinuation of selumetinib.

Table 18: List of Secondary objectives and endpoints

Secondary objective	Outcome measures
To determine the duration of response to selumetinib[a]	Duration of response (**DoR**) using centrally read volumetric MRI analysis
To determine progression-free survival (PFS) and time to progression (TTP)	**PFS** and **TTP** using centrally read volumetric MRI analysis
To determine the time to response (TTR)	**TTR** using centrally read volumetric MRI analysis

Secondary objective	Outcome measures
To determine PFS and TTP in the subgroup of patients with progressive PN (≥20% increase in PN volume within 12-15 months prior to enrolment), and compare PFS to the placebo arm of the tipifarnib study (01-C-0222; NCT00021541; Widemann et al. 2014)	• TTP and PFS in progressive PN (≥20% increase in PN volume within 12-15 months prior to enrolment) using centrally read volumetric MRI analysis • PFS in progressive PN (see previous bullet) compared to PFS in the placebo arm of the tipifarnib study
To characterise the effect of selumetinib on pain, quality of life, and physical functioning	Amongst others: **Pain**: NRS-11, pain medication survey and Pain Interference Index (PII) **Quality of life**: PedsQL
To determine the effect of selumetinib on **disfigurement**	Photography (+/- video) evaluation
To determine baseline functional impairments secondary to PN, and the effect of selumetinib on functional outcomes depending on PN location	Amongst others: **Motor PN:** MMT strength, ROM, PROMIS (mobility and upper extremity) **Airway PN:** functional evaluations (sleep studies, pulmonary function tests) **Bowel/bladder PN:** patient-reported outcomes (dysfunctional voiding questionnaire) **Orbit PN:** functional evaluations (vision, exophthalmometry)
To determine the effect of selumetinib on the PN growth rate based on volumetric analysis of MRI studies obtained prior to enrolment (if available and amenable to volumetric analysis)[b]	Volumetric analysis of **MRI studies obtained prior to enrolment** (if available and amenable to volumetric analysis)

[a] Duration of response was determined in those patients with a confirmed response.

[b] This objective was of exploratory nature for research purposes and data were not collected in the clinical database; therefore, no data were available.

ERK Extracellular signal related kinase; MRI Magnetic resonance imaging; MMT manual muscle test; NRS-11 Numerical rating scale-11; ORR Objective response rate; PBMC Peripheral blood mononuclear cells; PedsQL Paediatric Quality of Life Inventory; PFS Progression-free survival; PN Plexiform neurofibroma; PR Partial response; PROMIS Patient-reported outcomes measurement information system; REiNS Response evaluation in neurofibromatosis and schwannomatosis; ROM range of motion; SAP Statistical analysis plan; TTP Time to progression

Additional objectives and endpoints

An additional objective/endpoint was a comparison of PN growth rates and PFS in SPRINT Phase II Stratum 1 to the Natural History (NH) study (08-C-0079; NCT00924196), i.e. a descriptive evaluation. Patient data from the NH study were thus used as external control data.

Exploratory objectives and endpoints

An exploratory objective/endpoint was to assess the relationship between tumour volume/response and clinical outcome assessments (COAs), i.e. patient- (or parent) reported and functional outcomes.

First, correlations between COAs and PN volume at baseline were explored, as well as correlations between changes in COAs and changes in PN volume (assessed as percent change from baseline) at pre-Cycle 13. Secondly, the association between post-baseline longitudinal changes in COAs and changes in PN volume was evaluated.

Individual patient reviews (IPRs)

To characterise the efficacy of selumetinib at an individual patient level, patient data from SPRINT Phase II Stratum 1 were also presented in the format of individual patient reviews (IPRs). The aim of each IPR was to provide a comprehensive and cohesive narrative of the patient's journey prior to and during treatment with selumetinib, including an Investigator assessment of whether each patient derived clinical benefit from study treatment.

Sample size

The sample size for the primary objective of ORR in patients with PN-related morbidity was based on a target response rate to exclude 15% with a lower 2-sided 95% confidence bound. With 50 total evaluable

symptomatic patients, an exact binomial test with a nominal 1-sided 2.5% significance level had 90% power to detect the difference between a null hypothesis response rate of 15% and an alternative hypothesis response rate of 36%. With 14 or more responses out of the 50 patients, the lower limit of the exact 2-sided 95% confidence interval for the response rate would be 16.2% or greater. Thus, 14 or more responses in 50 evaluable patients was consistent with results that would statistically significantly exceed a 15% true response rate based on a 2-sided confidence interval.

Randomisation

This was a single-arm study.

Blinding (masking)

The study was open-label.

Statistical methods

Description of analysis populations/sets

Efficacy analyses related to assessing response in terms of volumetric reduction of target PN (ORR, DoR, TTR, PFS and TTP) were conducted on the full analysis set (FAS) that included all patients who received at least 1 dose of selumetinib. Unless stated otherwise by supplementary analyses, sources of data that have not contributed to the efficacy analyses included multiple partial volumes of target PN, off-schedule assessments and data collected after permanent discontinuation of selumetinib. COAs were conducted either on the FAS, or age-subsets of the FAS (pain in subset of patients ≥8 years, physical functioning in subset of patients ≥5 years) or a subset of the FAS with PN-related morbidity.

Primary endpoint: ORR analyses

Primary ORR analysis

Centrally read 3D MRI volumetric MRI analysis was performed by a single reviewer at the NCI POB, who was a leading expert in the REiNS Tumor Imaging working group. Response was assessed prior to Cycles 5, 9, 13, 17, 21, 25 and then after every 6 cycles until permanent discontinuation of selumetinib. Response assessment was based on evaluation of target PN only and followed the REiNS criteria (Dombi et al. 2013).

NCI POB Central analysis of PN response – Primary Analysis

At each scheduled pre-cycle assessment, patients were programmatically assigned a tumour response derived from volumetric MRI analysis of the target PN prior to Cycles 5, 9, 13, 17, 21, 25 and then after every 6 cycles until permanent discontinuation of selumetinib. In most instances, the entire PN was captured by volumetric MRI, but in some instances a partial volume measurement was collected (e.g., due to movement during MRI, presence of haematoma or metalwork) – in this instance partial volume measurements were used in the programmatic derivation of tumour response only when a single baseline partial volume was available, otherwise response was not calculated. Unscheduled volumetric MRI data (i.e., data that did not correspond to a pre-cycle scheduled visit) and data collected following permanent treatment discontinuation were not used in the programmatic derivation of tumour response. Supplementary analyses were performed to derive ORR and DoR based on all available volumetric MRI scans.

Independent Central Review (ICR) – Sensitivity Analysis

An independent review of volumetric MRIs was conducted (using target PN only), according to modified REiNS criteria (sensitivity analysis). The ICR was performed retrospectively, after DCO, on the complete set of scheduled volumetric MRIs (target PN only) for each patient. For the ICR, volumetric MRIs were assessed by either an independent whole body radiologist or a neuro-radiologist (2 radiologists and 1 neuro radiologist were available), with the involvement of imaging specialists. A written description of the target PN location was provided to to ensure the same PN was assessed for the ICR analysis. Since the target PN was considered by the site investigators to be the most clinically relevant PN causing morbidities at baseline, the independent reviewers needed to assess the same target PN as was assessed by the NCI POB central reviewer. However, the boundary selection of the target PN was still performed by , to maintain the independent review. Though the NCI POB and ICR analyses followed the same REiNS assessment criteria, there were some key differences in the ICR methodology in the handling of partial target PN volumes, image analysis methods and number of reviewers (NCI POB: single reviewer, ICR: choice of 3 reviewers) compared to the NCI POB central analysis. ORR and DoR analyses were generated and a concordance analysis was conducted to describe the NCI POB central analysis target PN responses in relation to the ICR analysis responses (based on REiNs). The margins of error for target PN volume at baseline and for percentage change from baseline were assessed using the intraclass correlation coefficient (ICC), which compared the assessment of 2 independent readers from on 10 randomly chosen patients.

Secondary endpoint: DoR analyses

Primary DoR analysis

Duration of response (**DoR**) was defined as the time from the pre-cycle volumetric MRI assessment of the first documented response (subsequently confirmed) until the pre-cycle volumetric MRI assessment of documented progression on treatment or death in the absence of disease progression. It was derived based on scheduled pre-cycle volumetric MRI assessments. The Kaplan-Meier (KM) method was used to amongst others calculate median DoR and 95% CI, and calculate the median time to onset of response from initiation of study treatment and 95% CI. Only patients who had a CR or confirmed PR were included in this analysis. DoR censoring followed the PFS censoring rules (

Table 24).

Sensitivity analyses

DoR was also derived based on the ICR according to REiNS criteria using the same statistical method as for the NCI POB central analysis.

A second sensitivity analysis using the actual dates of the NCI POB-based imaging assessments or death (if any) was conducted. DoR based on actual dates was defined as the time from the date of first documented (and subsequently confirmed) response until the date of documented progression or death in the absence of disease progression.

Secondary endpoint: PFS analysis

Progression-free survival (**PFS**) was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of objective disease progression on treatment or death (by any cause in the absence of progression). Median PFS with 95% CIs was calculated using a KM plot. The PFS censoring rules are summarised in Table 24.

Table 19: Summary of PFS censoring rules

Situation	Pre-cycle MRI assessment of PD/Death or Censoring	PFS Outcome
Death, Progressive Disease (PD)	Pre-cycle MRI assessment of earliest sign of PD (death date if the event is death)	Event
No PD or death at time of analysis or lost to follow-up	Latest evaluable pre-cycle MRI assessment	Censored
Death or PD after ≥ 2 missed assessments (for assessments occurring up to pre-cycle 25)	Latest evaluable pre-cycle MRI assessment prior to the two missed assessments.	Censored
Death or PD after ≥ 1 missed assessment (for assessments occurring from pre-cycle 31 onwards)	Latest evaluable pre-cycle MRI assessment prior to the one missed assessment.	Censored
No evaluable pre-cycle MRI assessment or no baseline data and no death within two cycles from baseline	Day 1	Censored
Death within two cycles from baseline	Death date	Event

Secondary endpoint: TTP analysis

Time to progression (**TTP**) was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of objective disease progression on treatment. Median TTP with 95% CIs was calculated using a KM plot. TTP censoring followed the PFS censoring rules (

Table 24).

Secondary endpoint: TTR analysis

Time to response (**TTR**) was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of the first documentation of CR or a subsequently confirmed PR. It was derived based on scheduled pre-cycle volumetric MRI assessments. The pre-cycle volumetric MRI assessment of the first documented response was to coincide with that used for the DoR endpoint. Median TTR with 95% CIs was calculated from a KM plot. Only patients who had achieved a CR or a confirmed PR were evaluated for TTR.

Secondary endpoint comparison of PFS in progressive PN in SPRINT Phase II Stratum 1 to PFS in placebo arm of tipifarnib study (descriptive evaluation)

For the design of the tipifarnib study and its use as external control for SPRINT Phase II Stratum 1, see Analyses performed across trials.

Additional endpoint comparison of PN growth rates and PFS in SPRINT Phase II Stratum 1 to PN growth rates and PFS Natural History study (descriptive evaluation)

For the design of the Natural History study and its use as external control for SPRINT Phase II Stratum 1, see Analyses performed across trials.

Statistical methods for functional evaluations

The following descriptive analyses were also provided, as applicable:

- A table with descriptive statistics for the observed values and the change from baseline in functional outcome as applicable; a line graph with mean of change from baseline values and corresponding 95% CI for each pre-cycle visit.

- Descriptive statistics (counts and percentages) for patients with improvement/no change/deterioration at each pre-cycle visit. The 95% confidence interval for a single binomial proportion were also provided.

- Change from baseline in the primary outcomes were further analysed using a Mixed model repeated measures (MMRM).

Table 20: Secondary objectives and corresponding clinical outcome assessments

Secondary objective	Instrument	Type of evaluation	Population
To determine the effect of selumetinib on:			
Pain	NRS-11 PII Pain medication survey	PRO	Subset of FAS aged ≥8 years Subset of FAS (self-report: ages 8 to 18 years; parent-report: ages 5 to 18 years) FAS
Health-related Quality of Life	PedsQL	PRO	FAS (self-report: ages 8 to 18 years; parent-report: ages 2 to 18 years)
To determine the effect of selumetinib on functional outcomes depending on PN location:			
Motor PN	MMT strength ROM	Functional	Subset of FAS with motor PN-related morbidity
	Mobility and upper extremity (PROMIS)	PRO	Subset of FAS with motor PN-related morbidity (self-report: ages 8 to 18 years; parent-report: ages 5 to 18 years)
Airway PN	Sleep studies[a] PFTs[b]	Functional	Subset of FAS with airway PN-related morbidity
Bowel/bladder PN	Bowel/bladder questionnaire	PRO	Subset of FAS with bowel/bladder PN-related morbidity
Orbit PN	Acuity testing Exophthalmometry	Functional	Subset of FAS with orbit PN-related morbidity

[a] Patients who have a tracheostomy which bypasses the airway obstruction caused by the PN do not require sleep study.
[b] Patients with a tracheostomy are not required to perform PFTs.
FAS Full analysis set; 6MWT 6-minute walk test; MMT manual muscle test; NRS-11 Numerical rating scale-11; PedsQL Paediatric Quality of Life Inventory; PFTs Pulmonary function tests; PII Pain interference index; PN Plexiform neurofibroma(s); PRO Patient-reported outcomes; PROMIS Patient-reported outcomes measurement information system; QoL Quality of life; ROM range of motion

For analysis of the PROs, the patient- and parent-reported data were analysed and presented separately. The primary analysis of the COAs was based on the descriptive statistics and MMRM models that summarised the changes over time. In addition, supportive analyses using clinically meaningful thresholds (CMTs) were conducted. These CMTs were estimated using both distribution- (one-half standard deviation) and anchor-based (with the global impression of change [GIC] as the anchor) approaches, supplemented with empirical cumulative distribution function (eCDF) and probability density function (PDF) curves. Whenever available, thresholds from published literature were also used. Regarding missing data, the COAs were analysed using the mixed model repeated measures (MMRM) under a missing at random (MAR) assumption.

A few COAs are described in brief below.

Pain intensity (NRS-11)

Pain intensity was measured by the Numerical Rating Scale-11 (NRS-11), consisting of 4 questions scored on a scale 0=no pain to 10=worst pain you can imagine. This pain rating was for the physician-selected target PN only.

Pain interference index (PII)

Pain interference was measured by the PII. The PII is a 6-item scale that assesses the extent to which pain has interfered with an individual's daily activities in the past 7 days. Items are rated on a 7-point Likert scale (0=not at all to 6=completely), and the total score is the mean of the completed items.

PedsQL

General Quality of Life (QoL) was measured using the generic Pediatric Quality of Life Inventory (PedsQL 4.0 Generic Core Scales). The generic PedsQL assesses function in 4 domains: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items) and 4) School Functioning (5 items). Each item is scored on a 5-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items were reverse-scored and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0), so that higher scores indicated better HRQoL.

Motor function

Analysis of motor function includes only those patients in the FAS with motor morbidity at enrolment.

Motor function was assessed by manual muscle test (MMT) strength for each muscle group (scale of 0 to 5 using the Medical Research Council scale) and range of motion (ROM) for joints (measured in degrees).

Motor function was also assessed using the Patient-Reported Outcome Measurement Information System (PROMIS) Pediatric Short Form v1.0 – Mobility 8a and PROMIS Pediatric Short Form v1.0 – Upper Extremity 8a. These forms assessed level of motor function over the past 7 days. The short forms consisted of 8 items using a 5-point Likert scale format (i.e., 0=unable to do, 4=can do without any difficulty). Raw scores were converted to T–scores, which are based on reference data from the US general population, where mean=50, SD=10. Higher scores indicated better physical functioning.

Global impression of change (GIC)

Global impression of change (GIC) in tumour pain, overall pain and tumour-related morbidities compared to baseline were measured by the GIC scale, consisting of 3 questions scored on a 7-point scale (1=Very much improved to 7=Very much worse), and was self-assessed by patients and also assessed by parents. The GIC was used as an anchor to derive clinically meaningful change thresholds as described above.

Correlation analyses

The following clinical outcome assessments were considered for the correlation analysis with target PN volume from baseline to pre-Cycle13:

- Pain intensity (NRS-11): patient-reported pain intensity score on the "target tumour"
- Pain interference index (PII): PII score
- Motor function (PROMIS): mobility and upper extremity scores
- HRQoL (PedsQL): the PedsQL total score and the four domain scores of physical functioning, emotional functioning, social functioning and school functioning.

The Spearman rank correlation coefficients (r), which measured strength of rank preserving relationship, were assessed per Cohen 1998. Whilst a weak correlation coefficient indicated a lack of evidence of a rank preserving relationship, it was not to be interpreted as lack of relationship in general.

- r = 0 to 0.3 equates to a weak correlation

- r = 0.3 to 0.5 equates to a moderate correlation

- r = 0.5 to 1.0 equates to a strong correlation.

A positive correlation was defined as both an improvement in the COA and a reduction in target PN volume.

Results

Participant flow

In total, 50 patients were enrolled and received at least 1 dose of selumetinib. At DCO (29 June 2018), 46 (92.0%) patients remained within the study; of these, 34 (68.0%) patients remained on selumetinib. The median follow-up time was 24 cycles.

Table 21 : Patient disposition (All patients)

	Number (%) of patients Selumetinib 25 mg/m² BID
Patients enrolled[a]	50
Patients who received at least one dose of selumetinib[b]	50 (100)
Patients ongoing selumetinib at data cutoff[c]	34 (68.0)
Patients who discontinued study treatment[c] :	16 (32.0)
Adverse Event	6 (12.0)
Disease progression on study	3 (6.0)
Investigator discretion	3 (6.0)
Treatment period completed	2 (4.0)
Patient not willing to continue treatment	1 (2.0)
Severe non-compliance to protocol	1 (2.0)
Patients ongoing study[c]	46 (92.0)
Patients who terminated study[c]	4 (8.0)
Voluntary discontinuation by patient	2 (4.0)
Lost to follow-up	1 (2.0)
Other	1 (2.0)

[a] Informed consent received.

[b] Percentages are calculated from number of patients who were assigned to selumetinib.

[c] Percentages are calculated from number of patients who received selumetinib.

BID Twice daily.

Recruitment

Recruitment of the 50 patients was done in 4 paediatric centres in the USA: Childrens National Medical Center, National Cancer Institute Pediatric Oncology Branch, Cincinnati Childrens Hospital and The Childrens Hospital of Philadelphia. The first patient was enrolled on 12 August 2015 and the last patient was enrolled on 22 August 2016.

Conduct of the study

Protocol amendments

The original protocol was dated 6-Apr-2011. The first 8 protocol amendments pertained to SPRINT Phase I, whereas SPRINT Phase II only came into effect following the 9th protocol amendment. The final version of the study protocol, i.e. following the 16th protocol amendment, was dated 14-Jan-2019.

Protocol deviations

Two patients (4.0%) had important protocol deviations identified prior to database lock for the DCO. One patient was taken off-study (on Day 64; following Cycle 1) due to non-compliance with protocol requirements. Another patient had a Grade 2 AE of LVEF decrease (result=52%; Day 226; Pre-Cycle 9); however, the ECHO was only repeated on Day 338, 16 weeks later and thus not 3 to 6 weeks after the initial finding as outlined in the protocol. No dose modification was required as a result of this AE and the patient was ongoing selumetinib treatment at DCO.

Baseline data

- Demographic characteristics

Table 22: Demographic and patient characteristics (FAS)

		Selumetinib 25 mg/m² BID (N=50)
Age, years[a]	n	50
	Mean (SD)	10.3 (3.92)
	Median (min, max)	10.2 (3.5-17.4)
Sex, n (%)	Male	30 (60.0)
	Female	20 (40.0)
Race, n (%)	White	42 (84.0)
	Black or African American	4 (8.0)
	Asian	1 (2.0)
	Unknown[b]	3 (6.0)
Height, cm	n	50
	Mean (SD)	133.78 (21.023)
	Median (range)	132.78 (100.3-171.2)
Weight, kg	n	50
	Mean (SD)	34.94 (16.484)
	Median (range)	29.55 (15.7-88.7)
BSA, m^2	n	50
	Mean (SD)	1.127 (0.3401)
	Median (range)	1.040 (0.67-1.93)

[a] Age was calculated using the date of informed consent.

[b] Unknown race refers to patients with race recorded as "Multiple race, specifics unknown". Two patients had a further description of "African American and Caucasian, no Asian descent".

BID Twice daily; BSA Body surface area; FAS Full Analysis Set; SD Standard deviation.

- Disease characteristics

Table 23: Disease characteristics (FAS)

		Selumetinib 25 mg/m² BID (N=50)
Time from diagnosis of NF1 to start of selumetinib (years)	n	48
	Mean (SD)	9.03 (4.148)
	Median (min max)	7.99 (2.0-16.5)
Time from diagnosis of PN to start of selumetinib (years)	n	45
	Mean (SD)	7.55 (3.822)
	Median (min max)	6.34 (0.7-16.5)
Target PN volume[a], mL	Mean (SD)	837.11 (925.011)
	Median (min, max)	487.50 (5.6-3820.0)
Target PN classification[b], n (%)	Typical	45 (90.0)
	Nodular	4 (8.0)
	Solitary nodular	1 (2.0)
Target PN status, n (%)	Progressive	21 (42.0)
	Non-progressive	15 (30.0)
	Unknown	14 (28.0)
Target PN morbidity assignment, n (%)[c]	Disfigurement	44 (88.0)
	Motor dysfunction	33 (66.0)
	Airway	16 (32.0)
	Bowel and/or bladder dysfunction	10 (20.0)
	Orbital (vision)	10 (20.0)
	Other dysfunction	12 (24.0)
Target PN pain present, n (%)	Yes	26 (52.0)
	No	22 (44.0)
	Missing	2 (4.0)
Number of target PN morbidities[d]	Median (min, max)	3.0 (1-4)
Target PN location, n (%)	Neck/trunk	12 (24.0)
	Trunk/extremity	12 (24.0)
	Head	9 (18.0)
	Head/neck	8 (16.0)
	Trunk	5 (10.0)
	Extremity	4 (8.0)
Lansky performance status score[e]	n	47
	Mean (SD)	86.8 (8.10)
	Median (min, max)	90 (70-100)

		Selumetinib 25 mg/m² BID (N=50)
Karnofsky performance status score[e]	n	3
	Mean (SD)	83.3 (5.77)
	Median (min, max)	80 (80-90)

[a] Includes one patient who only had partial volumes throughout the study.

[b] Classification based on imaging.

[c] Additional information was captured in the 'other dysfunction' field for morbidities not falling within the assigned categories. Assigned by investigator; patients can have more than one PN-related morbidity. The "Other dysfunction" category included patients with PN pain, swallowing, disfigurement and sensory neuropathy. Patients with PN pain were captured under the pain morbidity category (ie, pain present = yes) and sometimes also captured in the 'other dysfunction' field.

[d] Does not include symptoms recorded as 'other'. Pain was included as a PN-related morbidity.

[e] Lansky performance status was assessed in patients who were 16 years of age or younger and Karnofsky performance status was assessed in patients who were older than 16 years of age. Both the Lansky performance status and the Karnofsky performance status scores range from 10 to 100, with higher scores indicating better functioning.

BID Twice daily; FAS Full Analysis Set; PN Plexiform neurofibromas; SD Standard deviation.

- Symptoms at baseline

Forty-seven (94.0%) patients had at least 1 disease-related symptom at baseline and over two-thirds of these patients had either a maximum Grade 2, Grade 3 or Grade 4 symptom at baseline (22 [44.0%], 8 [16.0] and 4 [8.0%] patients, respectively). The Grade 4 symptoms at baseline included: tracheal obstruction extrinsic (2 [4.0%] patients), glaucoma, optic nerve disorder and respiratory failure (each in 1 [2.0%] patient).

The most commonly reported symptoms at baseline were muscular weakness (34.0%; Grade 3: 4.0%), limb asymmetry (32.0%; Grade 3: 4.0%), tumour pain (32.0%; Grade 3: 2.0%), joint range of motion decreased (26.0%; Grade 3: 8.0%) and scoliosis (26.0%; Grade 3: 6.0%).

Three patients had PN-related symptoms and clinical findings recorded as PN-related morbidities, as assigned by the investigator, at baseline and as medical history/examination findings.

- Treatment prior to study entry

Overall, 39 (78.0%) patients had received a prior treatment for PN and/or another NF1-related tumour, with most patients having had either a medical therapy or surgery, or both.

Table 24: Previous disease-related treatment modalities (FAS)

Previous treatment modalities:	Number (%) of patients Selumetinib 25 mg/m² BID (N=50)
Number (%) of patients with previous disease -related treatment modalities	39 (78.0)
Medical therapy [a]	31 (62.0)
Surgery [a,b]	28 (56.0)
Radiation	1 (2.0)

a Medical therapy directed at other NF1 tumours may also be included.
b Surgery included 4 patients who had one or two biopsies only and no other prior PN-related surgical procedures. Other NF1-related surgeries may also be included.

The 2 most common PN-directed medical treatments (>20% of patients) received by these patients were interferons (including peg-interferon) and imatinib. Eighteen patients had received a single medical therapy and the remaining patients had received multiple successive medical therapies.

In total, 28 (56.0%) patients had at least 1 prior PN-related or an NF1-related surgical procedure. The most common prior surgical procedure was 'nervous system neoplasm surgery', which was mostly PN debulking or resection from various body locations. Many of these patients had multiple prior PN resections.

Numbers analysed

In total, 50 patients were enrolled and received at least 1 dose of selumetinib. Patients were enrolled at 4 sites in the US.

Table 25: Analysis sets (All patients)

Analysis set	Number of patients Selumetinib 25 mg/m^2 BID (N=50)
Patients assigned to treatment	50
Patients included in Full Analysis Set	50
Patients included in Safety Analysis Set	50
Patients included in Pharmacokinetic Analysis Set	50

Outcomes and estimation

- **Primary endpoint ORR**

NCI POB Central analysis of PN response – Primary Analysis

Table 26: Best objective response: NCI POB central analysis (FAS)

Best objective response	**Number (%) of patients Selumetinib 25 mg/m^2 BID (N=50)**
Complete response	0
Confirmed partial response[a]	33 (66.0)
Unconfirmed partial response[b]	4 (8.0)
Stable disease[c]	11 (22.0)
Progression[d]	0
Not evaluable[e]	2 (4.0)

[a] Response required consecutive confirmation within 3 to 6 months after the criteria for first response were met. Partial response = a decrease in the volume of the target PN by 20% or more compared with baseline.
[b] Partial response was achieved but either no confirmation assessment was performed or a confirmation assessment was performed but the response was not confirmed.
[c] Insufficient volume change from baseline to qualify for either partial response or progressive disease.
[d] Increase in the volume of the target PN by 20% or more compared with baseline or the time of best response (maximal PN shrinkage) after documenting a partial response.
[e] Two patients did not contribute to efficacy analyses as they did not have any scheduled post-baseline volumetric MRI scans.
BID Twice daily; FAS Full Analysis Set; NCI National Cancer Institute; PN Plexiform neurofibroma(s); POB Pediatric Oncology Branch; REiNS Response evaluation in neurofibromatosis and schwannomatosis.

- **Secondary endpoint: Duration of response**

At the DCO, 32 of 33 patients with a response had been followed for at least 12 months from onset of response. Of the 33 responders, the probability of remaining in response after 12 cycles, estimated using the Kaplan-Meier method, was 100% and median DoR from onset of response was not reached. The actual number (percentage) of patients remaining in response after 12 and 24 cycles was 29 (87.9%) and 9 (27.3%), respectively. Only 2 patients who initially responded had progressed by the DCO.

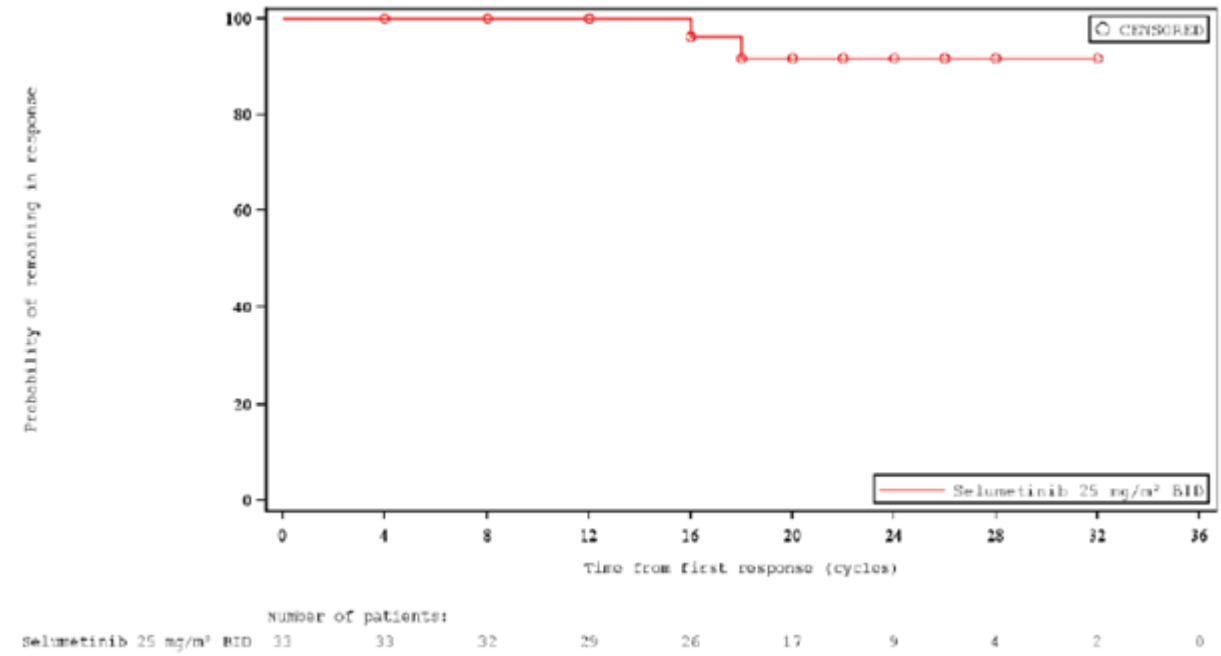


Figure 9: SPRINT Phase II Stratum 1 (pivotal data): Kaplan-Meier plot of DoR, NCI POB central analysis (REiNS; FAS)

- **Secondary endpoint: Progression free survival**

Median PFS in the FAS of SPRINT Phase II Stratum 1 was not reached; only 3 patients progressed at the DCO for study reporting (2 patients with best response of cPR and 1 patient had a best response of stable disease). No patients died.

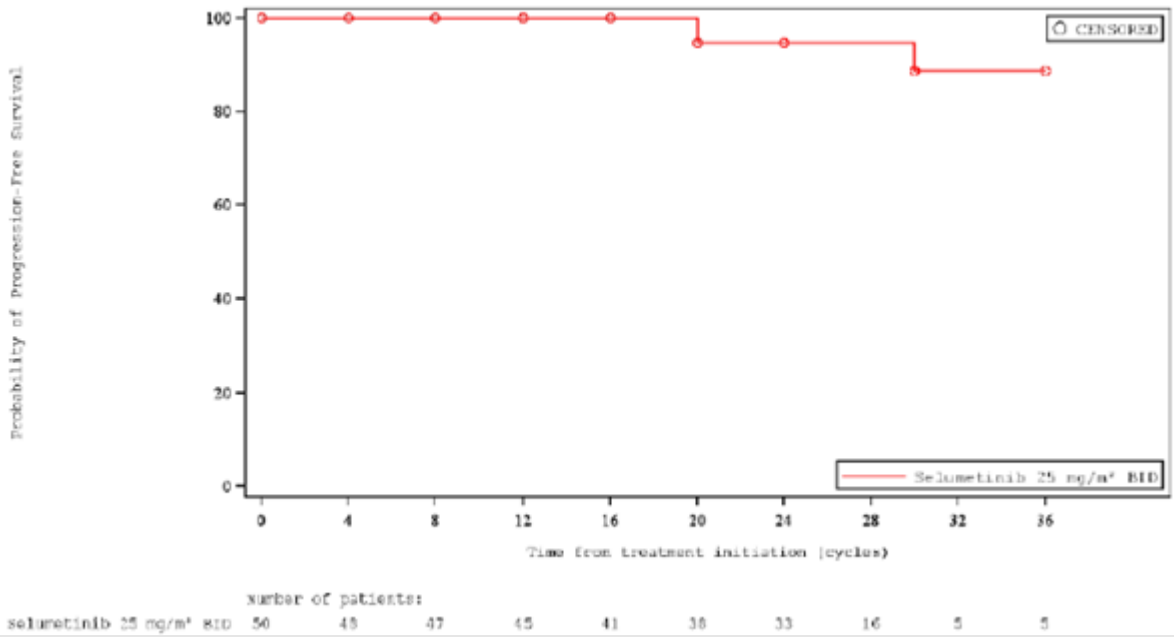


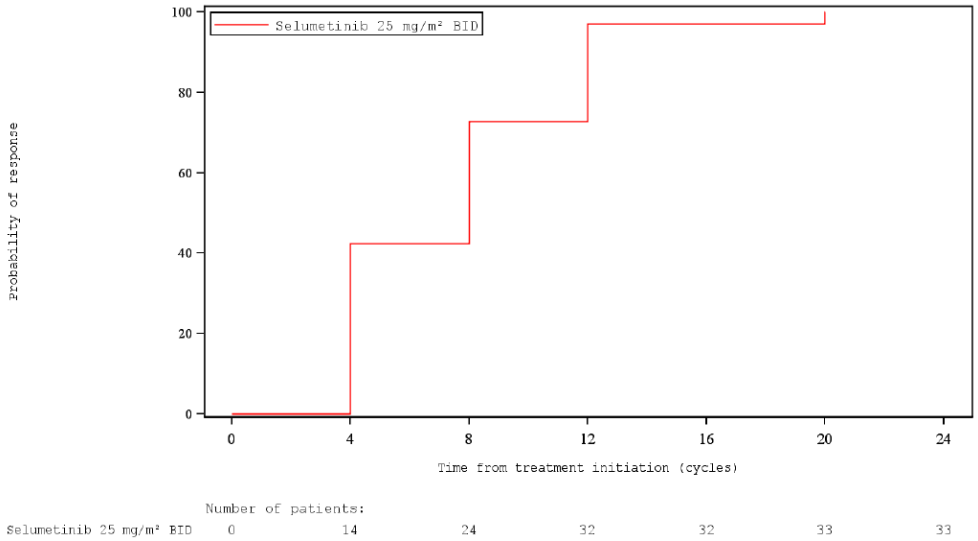
Figure 10: SPRINT Phase II Stratum 1 (pivotal data): Kaplan-meier plot of progression-free survival (PFS) – NCI POB central analysis (FAS)

- **Secondary endpoint: TTP**

In SPRINT Phase II Stratum 1, no patient had died at the DCO. Therefore, the TTP results are the same as the PFS results, see above.

- **Secondary endpoint: TTR**

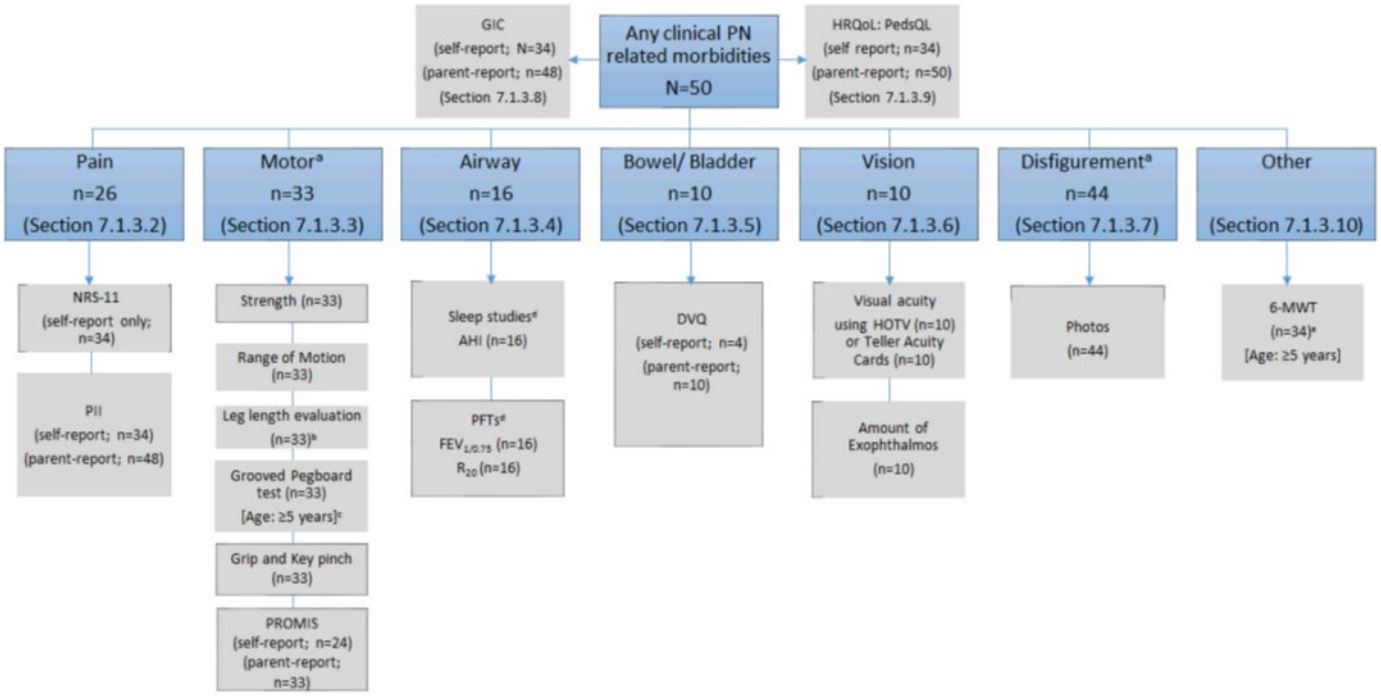
In the 33 responders, the median TTR was 8 cycles (95% CI: 4.0, 8,0), see Figure 11 which is a 1-KM plot of time to response of TTR. By 8 cycles from first dose, the majority of the responding patients (24 [72.7%] patients) had their response.



Time to response (TTR) is defined as the time from study treatment initiation until the pre-cycle of the first documentation of complete response or a subsequently confirmed partial response.
Only patients who have achieved a confirmed partial response will be evaluated for TTR.
The values at the base of the figure indicate number of patients who have responded by a given cycle.
Dots represent censored observations.
A cycle was defined as 28 days.
FAS Full Analysis Set; TTR Time to response.

Figure 11: 1-KM plot of TTR: NCI POB central analysis (FAS)

- **Secondary endpoint: Clinical outcome assessments**



a Videos were also recorded for some patients and are included within the individual patient reviews (data on file).
b Subset of FAS with PN located in the lumbosacral plexus or below (ie, lower limb)
c Subset of FAS ≥5 years at enrolment with PN located in the upper extremities or patients with known cervical or upper thoracic cord compression
d Patients who had a tracheostomy that bypassed the airway obstruction caused by the PN were not required to perform a sleep study or PFTs.
e Includes patients with lower extremity PN or cord compression irrespective of an airway PN.
Note: Photos are included within the individual patient reviews (data on file)
AHI Apnoea-Hypopnoea Index; CSP Clinical study protocol; DVQ Dysfunctional voiding questionnaire; FAS Full Analysis Set; FEV1/0.75 Forced expiratory volume in 1 second/0.75 seconds; GIC Global Impression of Change; HRQoL Health-related quality of life; 6MWT 6-Minute walk test; NRS Numerical rating scale; PedsQL Paediatric Quality of Life Inventory; PFT Pulmonary function test; PII Pain interference index; PMS Pain medication survey; PN Plexiform neurofibroma(s); PROMIS Patient-reported outcomes measurement information system; R Resitance; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis; SAP Statistical analysis plan.

Figure 12: Clinical outcome assessments: flowchart

1. **<u>Pain evaluations</u>**

<u>Pain intensity (NRS-11)</u>

Of the 24 patients, with physician-selected target tumour scores, who completed both baseline and pre-Cycle 13 assessments, 12 (50.0%) patients showed improvement of ≥2 points (which was used as a clinically meaningful change [CMT]). Of the 12 (50.0%) patients who showed no change, 10 patients had a pain score of 0 or 1 at baseline and therefore had no possibility to improve by 2 points or more.

Table 27: Change from baseline for NRS-11 pain intensity primary outcome

	Selumetinib 25 mg/m² BID (N=34)					
Parameter	Statistic	Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle13	Pre-Cycle25
Physician-selected target tumour pain	n	25	25	25	24	18
	Adjusted mean	-1.28	-1.41	-1.83	-2.07	-2.32
	Standard error	0.270	0.345	0.265	0.368	0.474
	95% CI	-1.84, -0.72	-2.13, -0.70	-2.38, -1.28	-2.84, -1.31	-3.34, -1.30
	p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001

[a] Nominal p-value

The model included terms for pre-cycle, baseline score, age, the number of morbidities at baseline and baseline X pre-cycle interaction.

Note: Patients aged 8 to 18 years at enrolment completed self-report measures of the NRS-11.

Patients who had their baseline evaluation using an earlier version of the NRS-11, which did not yet include the target tumour item, were considered only if self-selected and target tumour (PN) were the same.

BID Twice daily; CI Confidence interval; FAS Full Analysis Set; MMRM Mixed Model Repeated Measures; NRS-11 Numeric rating scale-11; PN Plexiform neurofibroma.

Correlation analysis: NRS-11 target tumour pain intensity score – target PN volume

Correlation analysis with change from baseline in target PN volume was evaluated for the subset of patients with a NRS-11 target tumour pain intensity score of 2 or more at baseline; as no improvement can be expected from patients with no pain at baseline, to assess the correlation between change in NRS-11 and percent change in target PN volume from baseline to pre-Cycles 5, 9, 13 and 25.

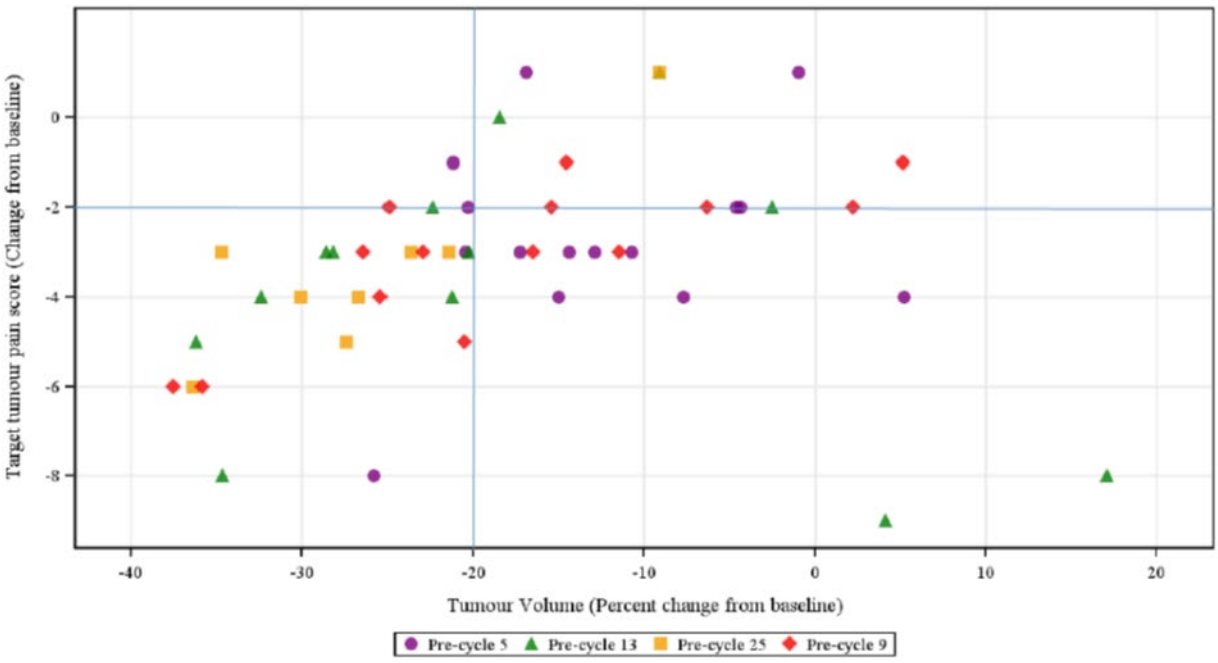


Figure 13: Correlation between change in NRS-11, in patients with a target tumour pain intensity score of 2 or more at baseline, and percent change in target PN volume from baseline to pre-Cycles 5, 9, 13 and 25 (FAS)

- Pre-Cycle 5 Spearman rank correlation coefficient = 0.07 (weak)
- Pre-Cycle 9 Spearman rank correlation coefficient = 0.76 (strong)
- Pre-Cycle 13 Spearman rank correlation coefficient = 0.13 (weak)
- Pre-Cycle 25 Spearman rank correlation coefficient = 0.71 (strong).

Pain interference index (PII)

PII was parent-reported for patients aged 5 and above and self-reported for patients aged 8 and above

Of the 29 patients who completed both baseline and pre-Cycle 13 assessments by self-reporting, 10 (34.5%) patients showed improvement of ≥0.75 (CMT). Of the 18 (62.1%) patients who showed no change, 15 patients had a baseline score <0.75 and therefore could not improve by 0.75 or more. One (3.4%) patient showed deterioration at pre-Cycle 13.

Of the 42 parents who completed both baseline and pre-Cycle 13 assessments by parent-reporting, 14 (33.3%) patients showed improvement of ≥1.78 (CMT). Of the 25 (59.5%) patients who showed no change, 22 patients had a baseline score <1.78 and therefore could not improve by 1.78 or more. Three (7.1%) patients showed deterioration at pre-Cycle 13.

Table 28: Change from baseline for PII primary outcome, MMRM (FAS)

Parameter	Statistic	Selumetinib 25 mg/m² BID				
		Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle 13	Pre-Cycle 25
PII self-report, total score (n=34)	n	31	31	31	29	23
	Adjusted mean	-0.38	-0.46	-0.57	-0.65	-0.65
	Standard error	0.180	0.158	0.179	0.115	0.184
	95% CI	-0.75, -0.01	-0.78, -0.13	-0.93, -0.20	-0.89, -0.42	-1.02, -0.27
	p-value[a]	0.045	0.007	0.004	<0.001	0.002
PII parent-report, total score (n=48)	n	45	43	45	42	33
	Adjusted mean	-0.67	-0.71	-0.63	-0.82	-0.78
	Standard error	0.130	0.165	0.170	0.172	0.152
	95% CI	-0.93, -0.41	-1.04, -0.37	-0.98, -0.29	-1.17, -0.47	-1.09, -0.47
	p-value[a]	<0.001	<0.001	<0.001	<0.001	<0.001

a Nominal p-value
The model included terms for pre-cycle, baseline score, age, the number of morbidities at baseline, and baseline X pre-cycle interaction.
Note: Patients aged 8 to 18 years at enrolment completed self-report measures of the PII. Parents or legal guardians of children aged 5 to 18 years at enrolment completed the parent proxy PII.
BID Twice daily; CI Confidence interval; FAS Full Analysis Set; MMRM Mixed Model Repeated Measures; PII Pain interference index.

Correlation analysis: Pain interference scores – target PN volume

Table 29: Correlation between change in PII self- and parent-report pain interference scores and change in target PN volume from baseline to pre-Cycle 13 (FAS)

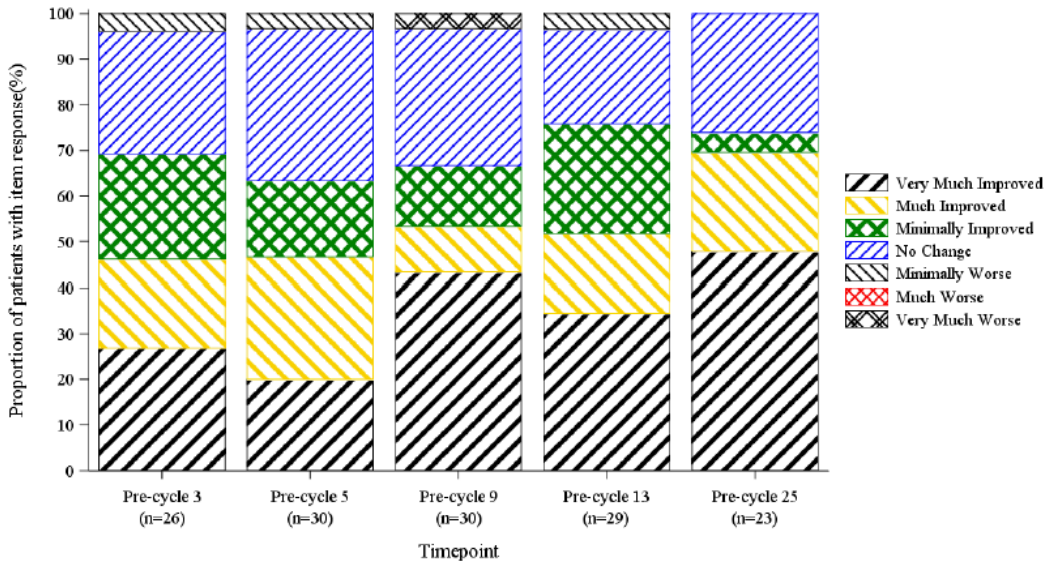
Parameter	Statistic	Selumetinib 25 mg/m² BID
PII self-report, total score (n=34)[a]	n	28
	r[c]	-0.40
	95% CI	-0.67, -0.02
	p-value	0.034
PII parent-report, total score (n=48)[b]	n	40
	r[c]	0.09
	95% CI	–0.23, 0.39
	p-value	0.576

a. Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the PII.
Patient 1019020 was too cognitively impaired to complete the self-report measures of the PII.
b Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the PII.
c Spearman rank correlations. Correlations with an absolute value greater than 0.3 indicate an adequate anchor (Coon and Cook 2018).
n = number of patients with both a PII score and change in target PN volume recorded at pre-Cycle 13.

Global impression of change (GIC)

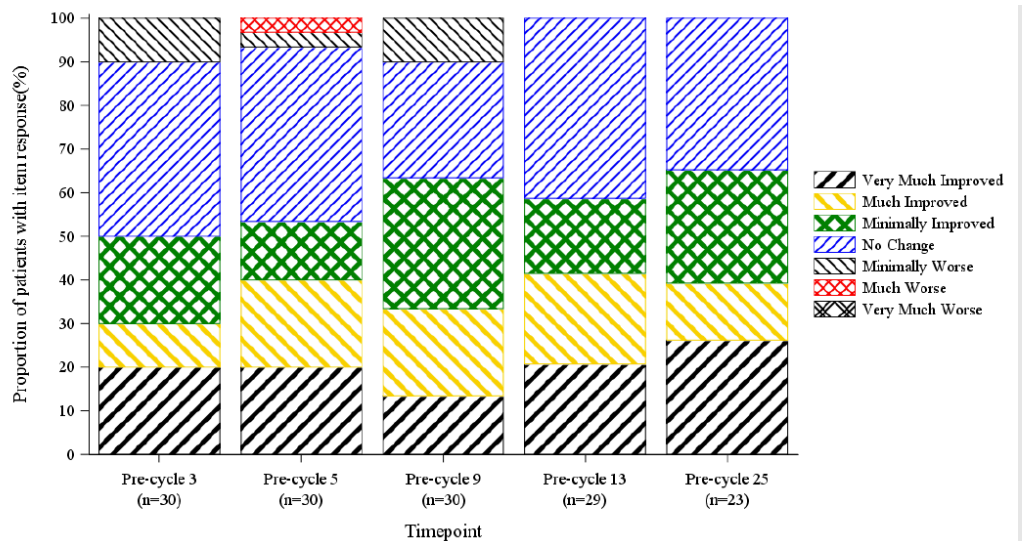
- *Self-report*

Figure 14 summarises the distribution of GIC **self-report** responses over time for the response category of **tumour pain**.



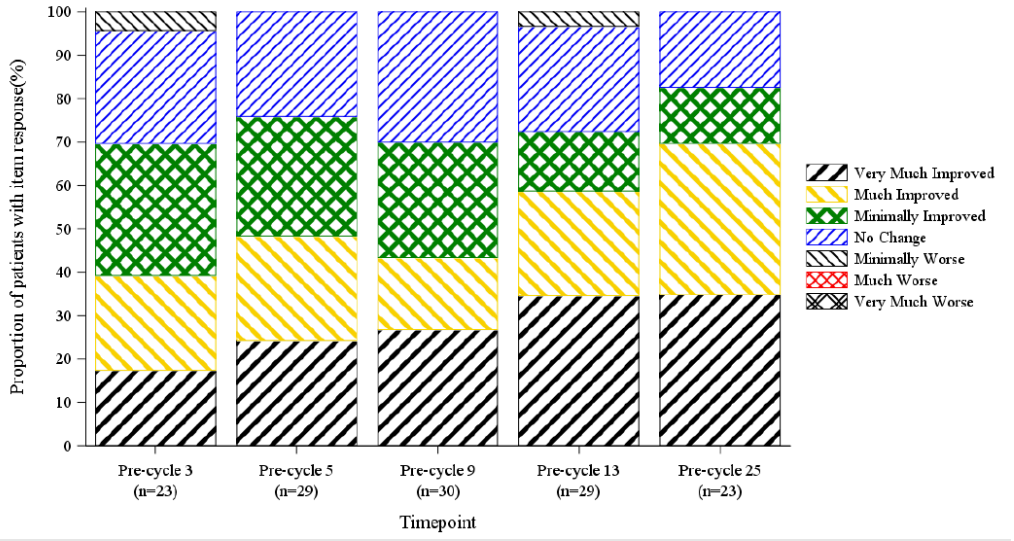
Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the GIC (n=34).
GIC Global impression of change.
Figure 14: Distribution of GIC self-report item responses over time: tumour pain (FAS)

Figure 15 summarises the distribution of GIC **self-report** responses over time for the response category of **overall pain**.



Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the GIC (n=34).
GIC Global impression of change.
Figure 15: Distribution of GIC self-report item responses over time: overall pain (FAS)

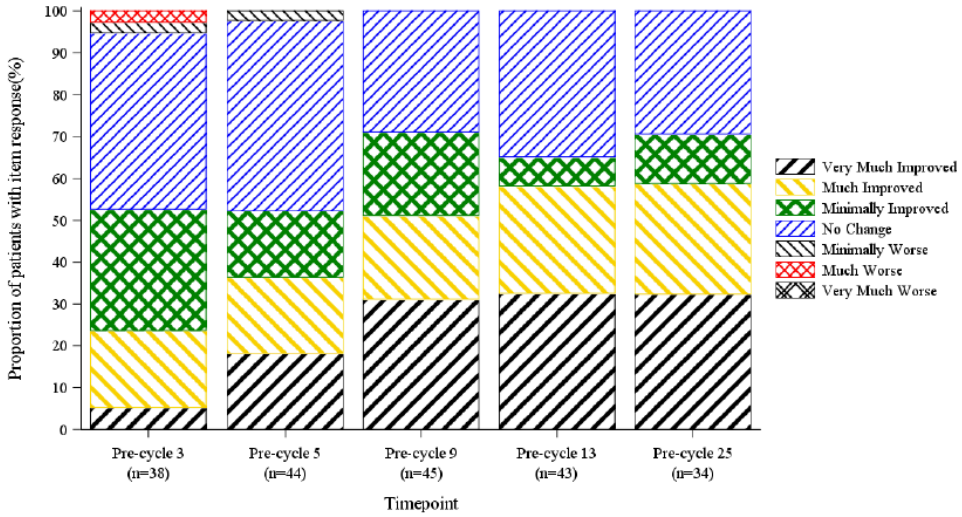
Figure 16 summarises the distribution of GIC **self-report** responses over time for the response category of **tumour-related morbidity other than pain**.



Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the GIC (N=34).
FAS Full Analysis Set; GIC Global impression of change
Figure 16: Distribution of GIC self-report item responses over time: tumour-related morbidity (FAS)

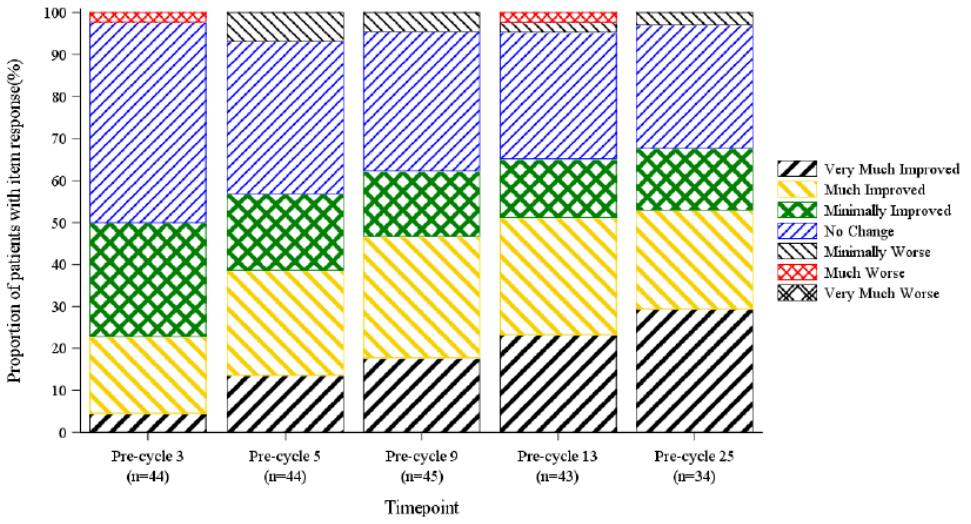
- *Parent-reported*

Figure 17 summarises the distribution of GIC **parent**-reported responses over time for the response category of **tumour pain**.



Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC (n=48).
FAS Full Analysis Set; GIC Global impression of change.
Figure 17: Distribution of GIC parent-reported item responses over time: tumour pain (FAS)

Figure 18 summarises the distribution of GIC **parent**-reported responses over time for the response category of **overall pain**.

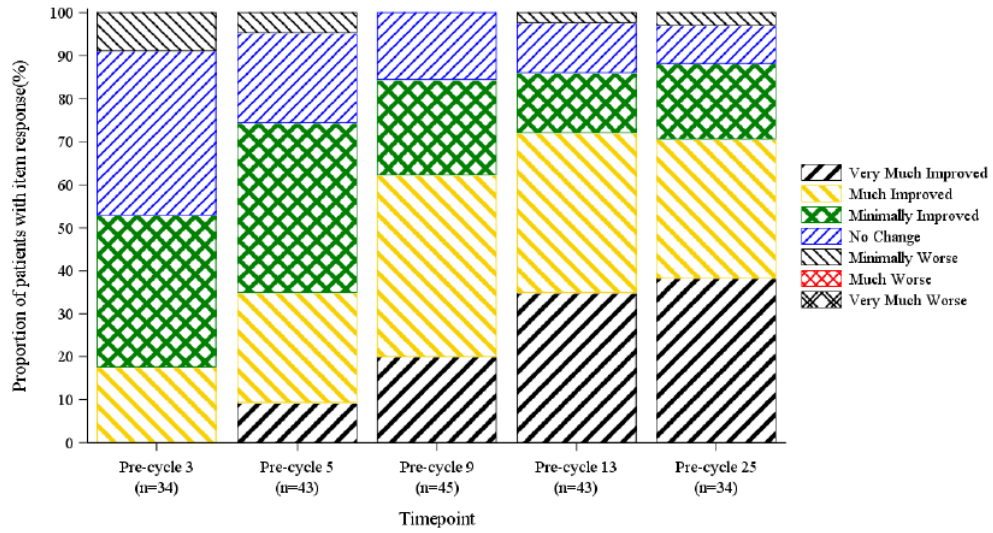


Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC (N=48).

Figure 18: Distribution of GIC parent-report item responses over time: overall pain (FAS)

- *GIC Global impression of change*

Figure 19 summarises the distribution of GIC **parent**-reported responses over time for the response category of **tumour-related morbidity other than pain**.



Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC (N=48).
FAS Full Analysis Set; GIC Global impression of change

Figure 19: Distribution of GIC parent-report item responses over time: tumour related morbidity (FAS)

2 Motor function: Motor PN

The motor function in all motor morbidity patients were also assessed using the Patient–Reported Outcome Measurement Information System (PROMIS). This physical functioning questionnaire assessed level of motor function over the past 7 days.

PROMIS

Twenty-four patients were expected to complete PROMIS based on presence of a motor morbidity and age of 8 to 18 years at enrolment; of these, 23 and 22 patients had baseline values for mobility and

upper extremity, respectively. In addition, 33 parents were expected to complete PROMIS for their child based on presence of a motor morbidity and age of 5 to 18 years at enrolment; of these, 32 and 31 patients had baseline values for mobility and upper extremity, respectively, as completed by their parents.

Table 30: Change from baseline for PROMIS primary outcomes, MMRM (FAS with motor PN-related morbidity)

A: Self-report

Parameter	Statistic	Selumetinib 25 mg/m² BID				
		Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle 13	Pre-Cycle 25
Mobility: self-report[a]	n	21	22	22	20	14
	Adjusted mean	0.69	1.83	1.01	1.75	3.38
	Standard error	1.481	1.204	1.469	1.163	1.905
	95% CI	-2.44, 3.82	-0.69, 4.35	-2.06, 4.08	-0.70, 4.19	-0.93, 7.68
	p-value[b]	0.647	0.145	0.500	0.151	0.110
Upper extremity: self-report[a]	N	21	21	21	19	13
	Adjusted mean	0.34	-0.09	-1.40	1.76	2.31
	Standard error	1.419	0.950	1.627	1.255	1.699
	95% CI	-2.64, 3.32	-2.10, 1.92	-4.82, 2.03	-0.88, 4.39	-1.30, 5.92
	p-value[b]	0.814	0.928	0.402	0.179	0.193

a Patients aged 8 to 18 years at enrolment expected to complete self-report measures of the PROMIS (N=24).
b Nominal p-value.
The model included terms for pre-cycle, baseline score, age, the number of morbidities at baseline and baseline X pre-cycle interaction.
BID Twice daily; CI Confidence interval; FAS Full Analysis Set; MMRM Mixed Model Repeated Measures; PN Plexiform neurofibroma(s).

B: Parent-report

Parameter	Statistic	Selumetinib 25 mg/m² BID				
		Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle 13	Pre-Cycle 25
Mobility: parent-report[a]	n	30	30	31	28	19
	Adjusted mean	1.82	1.97	2.32	2.75	4.22
	Standard error	0.525	1.027	0.982	0.840	1.255
	95% CI	0.74, 2.90	-0.15, 4.08	0.31, 4.33	1.02, 4.48	1.61, 6.84
	p-value[b]	0.002	0.067	0.025	0.003	0.003
Upper extremity: parent-report[a]	n	30	29	30	27	18
	Adjusted mean	-0.23	0.81	-0.33	1.53	4.56
	Standard error	1.237	0.912	1.203	1.255	1.330
	95% CI	-2.78, 2.31	-1.06, 2.69	-2.79, 2.14	-1.06, 4.12	1.74, 7.37
	p-value[b]	0.853	0.380	0.788	0.235	0.003

a Parents or legal guardians of patients aged from 5 to 18 years at enrolment expected to complete the parent proxy PROMIS (N=33).
b Nominal p-value.
The model included terms for pre-cycle, baseline score, age, the number of morbidities at baseline and baseline X pre-cycle interaction.
BID Twice daily; CI Confidence interval; FAS Full Analysis Set; MMRM Mixed Model Repeated Measures; PN Plexiform neurofibroma(s).

The CMTs used for analysis of PROMIS are presented below.

Score	Self-report	Parent-report
Mobility	2.26 (raw score)	3.36 (raw score)
Upper extremity	3.73 (raw score)	4.64 (raw score)

There was a trend towards improvement in mobility (as rated by parents) at each time point and a trend towards improvement in upper extremity physical function at pre-Cycle 25. Some patients showed improvement on self-reported mobility total scores (6 of 20 patients, 30.0%) and upper extremity scores (5 of 19 patients, 26.3%), some patients showed deterioration from baseline to pre-Cycle 13 for the self-reported mobility and upper extremity scores (2 patients each).

A similar trend was observed for patients-reported scores, where some patients showing improvement on mobility total scores (9 of 28 patients, 32.1%) and upper extremity scores (4 of 27 patients, 14.8%)

Several patients had a score that was too high at baseline and therefore could not improve by the required CMT.

Correlation between PROMIS and PN volume

Table 31: Correlation between change in PROMIS self- and parent-report scores and percent change in target PN volume from baseline to pre-Cycle 13 (FAS with motor PN-related morbidity)

Parameter	Statistic	Selumetinib 25 mg/m² BID	
		Raw score	T-score
Mobility self-report score (n=24)[a]	n	20	20
	r[c]	0.03	0.11
	95% CI	-0.42, 0.46	-0.35, 0.52
	p-value	0.905	0.652
Mobility parent-report score (n=33)[b]	n	27	27
	r[c]	-0.48	-0.43
	95% CI	-0.72, -0.12	-0.69, -0.05
	p-value	0.010	0.023
Upper extremity self-report score (n=24)[a]	n	19	19
	r[c]	-0.19	-0.30
	95% CI	-0.59, 0.30	-0.66, 0.19
	p-value	0.454	0.220
Upper extremity parent-report score (n=33)[b]	n	26	26
	r[c]	-0.27	-0.16
	95% CI	-0.59, 0.14	-0.51, 0.25
	p-value	0.192	0.443

a Patients aged 8 to 18 years at enrolment, with a motor PN-related morbidity, expected to complete self-report measures of the PROMIS physical functioning questionnaire.
b Parents or legal guardians of patients aged 5 to 18 years at enrolment, with a motor PN-related morbidity, expected to complete the parent proxy measures of the PROMIS physical functioning questionnaire.
c Spearman rank correlations. Correlations with an absolute value greater than 0.3 indicate an adequate anchor (Coon and Cook 2018).
n = number of patients with both a score and change in target PN volume recorded at pre-Cycle 13.

The Spearman rank coefficient (r) for self-report was 0.11, which indicated a weak correlation between the change in PROMIS self-report score (mobility) and change in target PN volume. The Spearman rank coefficient (r) for parent-reported was -0.43, which indicated a moderate positive correlation between the change in PROMIS parent-report score (mobility) and change in target PN volume. This correlation for parent-reported scores suggests that increasing PROMIS T-scores, which indicate better physical functioning, were associated with decreasing target PN volumes. Based on the scatterplots, the majority of patients or their parents reported no change or improvement in PROMIS mobility scores when target PN volume decreased.

The Spearman rank coefficients (r) for self-reported was -0.30, which indicated a moderate positive correlation and, for the parent-reported was -0.16, which indicated a weak positive correlation between the PROMIS scores (upper extremity) and change in target PN volume. Most patients with decreased target PN volume also reported either no change or improvement in PROMIS upper extremity scores, and the parent-reported scores were similar based on the scatterplots.

6-minute walk test

Patients with lower extremity PN, cord compression, or airway PN did not demonstrate an overall mean change from baseline in the 6-minute walk test at pre-Cycle 13.

3. Disfigurement

Disfigurement was measured by standardised photography for all patients who had disfigurement assigned as a PN-related morbidity at baseline and at all re staging visits. These images were anonymised to ensure that patients could not be identified and genitalia was also respectfully treated. There was no formally planned method of assessing changes in disfigurement.

Forty-four patients (88%) had disfigurement and only 3 patients had this as their sole morbidity. This was the most common morbidity and, given the age of the patients, it was difficult to evaluate the impact physically and on the patients' well-being. Individual patient reviews were generated to ascertain improvement on a patient-by-patient basis, since it was not possible to summarise this at a population level.

4. Health-related Quality of Life (HRQoL): PedsQL

Based on self-reported PedsQL total scores, there were 11/33 patients with impaired global HRQoL at baseline. At pre-Cycle 13, there were 9 out of 29 patients with impaired HRQoL. For the 29 patients at pre-Cycle 13, 11 (37.9%) patients showed improvement of ≥10.33 (CMT). Of the 12 (41.4%) patients who showed no change, 2 patients had a total score of >89.67 at baseline and therefore had no possibility to improve by ≥10.33 (maximum PedsQL total score = 100).

Based on parent-reported PedsQL total scores, there were 28 out of 50 patients with impaired HRQoL at baseline. At pre-Cycle 13, there were 16 out of 45 patients with impaired HRQoL. For the 45 patients at pre-Cycle 13, based on a CMT of 11.90, 24 (53.3%) patients showed improvement. Of the 20 (44.4%) patients who showed no change, 2 patients had a total score of >88.10 at baseline and therefore had no possibility to improve by ≥11.90 (maximum PedsQL total score = 100). One (2.2%) patient showed deterioration at pre-Cycle 13.

Individual patient reviews (data not shown)

Patient data from SPRINT Phase II Stratum 1 were also presented in the format of individual patient reviews to characterise the efficacy of selumetinib at an individual patient level. The aim of each IPR was to provide a narrative of the patient's journey prior to and during treatment with selumetinib, including an investigator assessment of whether each patient derived clinical benefit from study treatment.

Each IPR includes programmed tables and figures, baseline volumetric MRI images of the target PN, anonymised photographs, links to anonymised baseline and pre-Cycle 13 videos (for each consenting patient with visible PN), and sections of handwritten text. Each IPR was concluded with a brief overview of the key efficacy and tolerability observations during the study, provided by an AstraZeneca physician. For each patient, the relevant Investigator determined whether or not the patient had obtained clinical benefit, as described in the IPR charter.

Ancillary analyses

First Independent Central Review (ICR) – Sensitivity Analysis

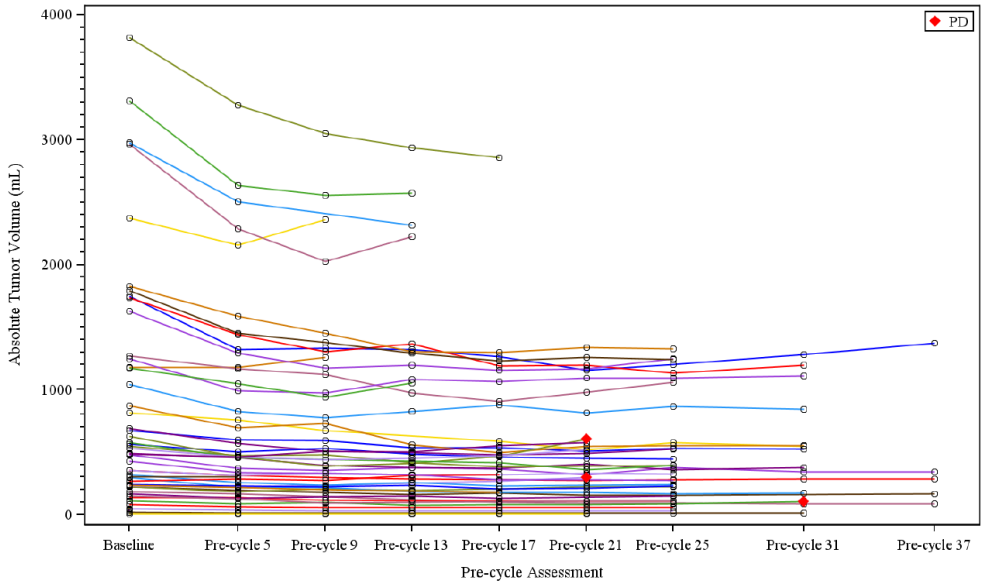
Table 32: Best objective response: ICR analysis (FAS)

Best objective response	Number (%) of patients Selumetinib 25 mg/m² BID (N=50)
Complete response	0
Confirmed partial response[a]	22 (44.0)
Unconfirmed partial response[b]	5 (10.0)
Stable disease[c]	21 (42.0)
Progression[d]	0
REiNS progression	0
Death	0
Not evaluable[e]	2 (4.0)

a Response required consecutive confirmation within 3 to 6 months after the criteria for first response were met. Partial response = a decrease in the volume of the target PN by 20% or more compared with baseline.
b Partial response was achieved but either no confirmation assessment was performed or a confirmation assessment was performed but the response was not confirmed.
c Insufficient volume change from baseline to qualify for either partial response or progressive disease.
d Increase in the volume of the target PN by 20% or more compared with baseline or the time of best response (maximal PN shrinkage) after documenting a partial response.
e Two patients did not contribute to efficacy analyses as they did not have any scheduled post-baseline volumetric MRI scans.

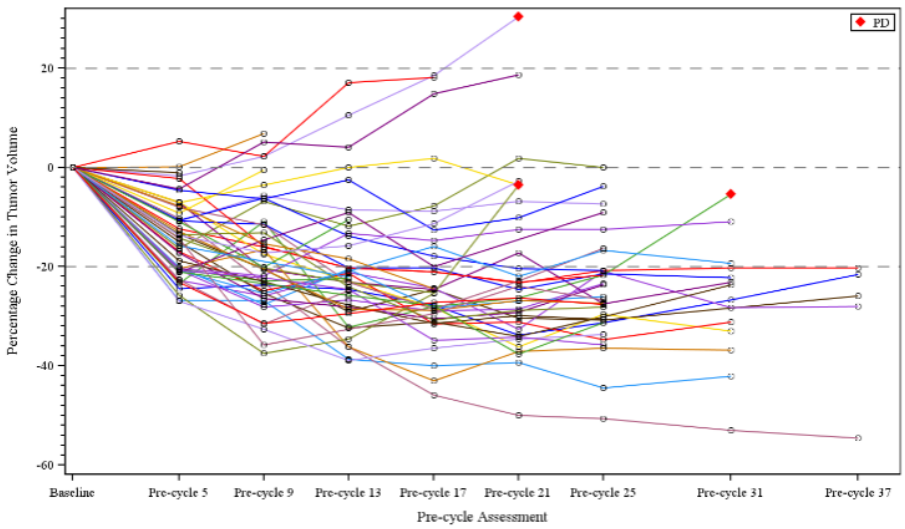
Target PN volume changes over time

The Figure 20 shows each patient's target PN volume over time with progression indicated.



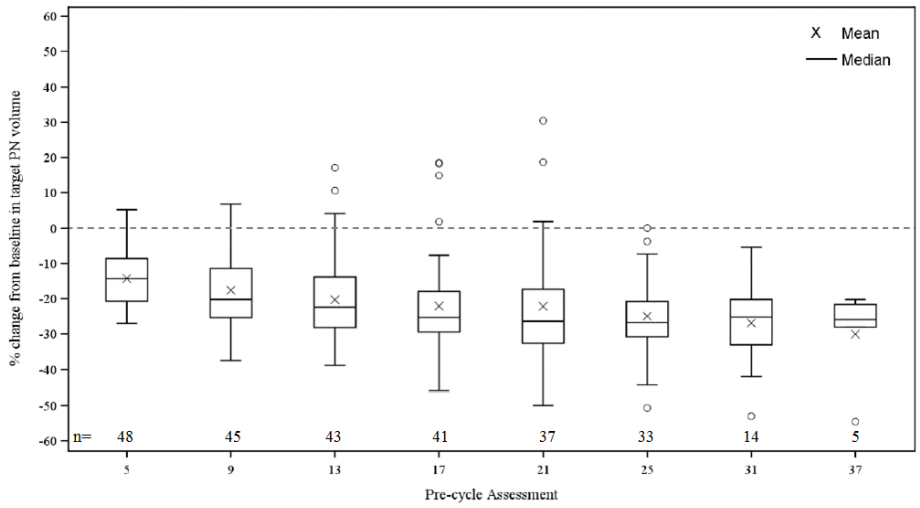
FAS Full Analysis Set; PD Progressive disease; PN Plexiform neurofibroma
Progressive disease is defined as an increase in the target PN volume by ≥20% compared to baseline or compared to the time of maximal tumour shrinkage after documenting a PR.
Figure 20: Target PN volume, individual patient data over time: NCI POB central analysis (FAS)

The Figure 21 shows each patient's percentage change in target PN volume over time with progression indicated.



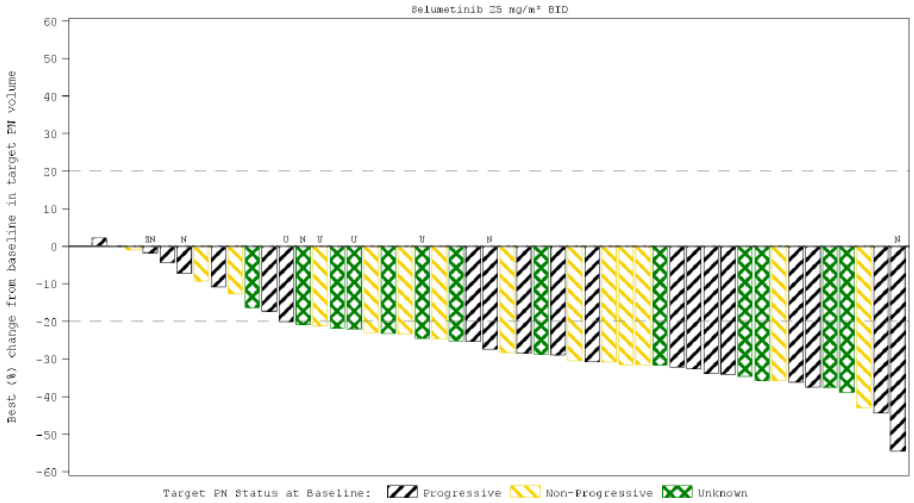
FAS Full Analysis Set; PD Progressive disease; PN Plexiform neurofibroma
Progressive disease is defined as an increase in the target PN volume by ≥20% compared to baseline or compared to the time of maximal tumour shrinkage after documenting a PR.
Figure 21: Percentage change in target PN volume, individual patient data over time: NCI POB central analysis (FAS)

The reduction in percentage change from baseline in target PN volume over time is shown in the box plot in Figure 22.



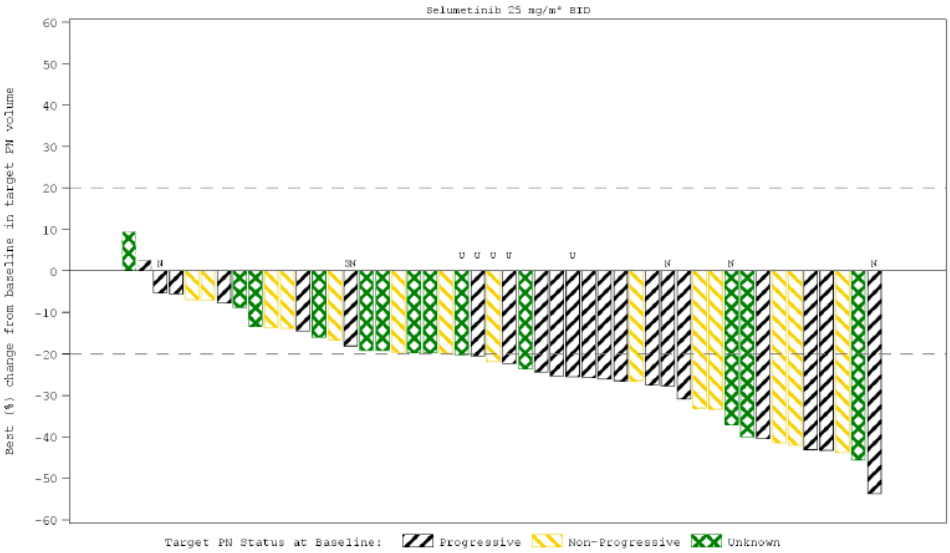
Horizontal line: Median, Box : Q1-Q3
Whiskers extend to the most extreme observation within 1.5 times the interquartile range from the nearest quartile, so that all outliers >1.5 times the interquartile range are individually displayed.
Figure 22: Percent change from baseline in target PN volume over time: NCI POB central analysis (FAS)

The best percentage change from baseline is presented graphically in Figure 23. The median best percentage change from baseline in target PN volume was -27.85% (range: -54.5 to 2.2; mean: -25.28% [SD 12.330]).



Best percentage change in target PN size is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. Bars not annotated with SN or N represent typical nodular PN. Includes a patient who only has partial volumes throughout the study.
FAS Full Analysis Set; PN Plexiform neurofibroma(s): N Nodular PN; SN Solitary nodular PN; U Unconfirmed response.

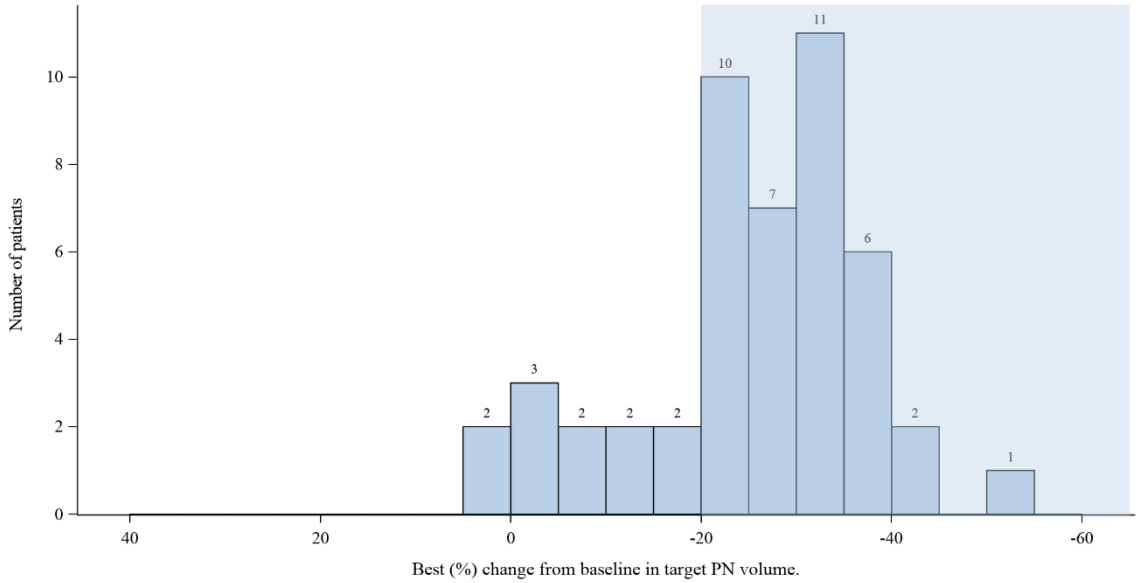
Figure 23: SPRINT Phase II Stratum 1 (pivotal data): Best percentage change from baseline in target PN volume - NCI POB central analysis - Waterfall plot (FAS)



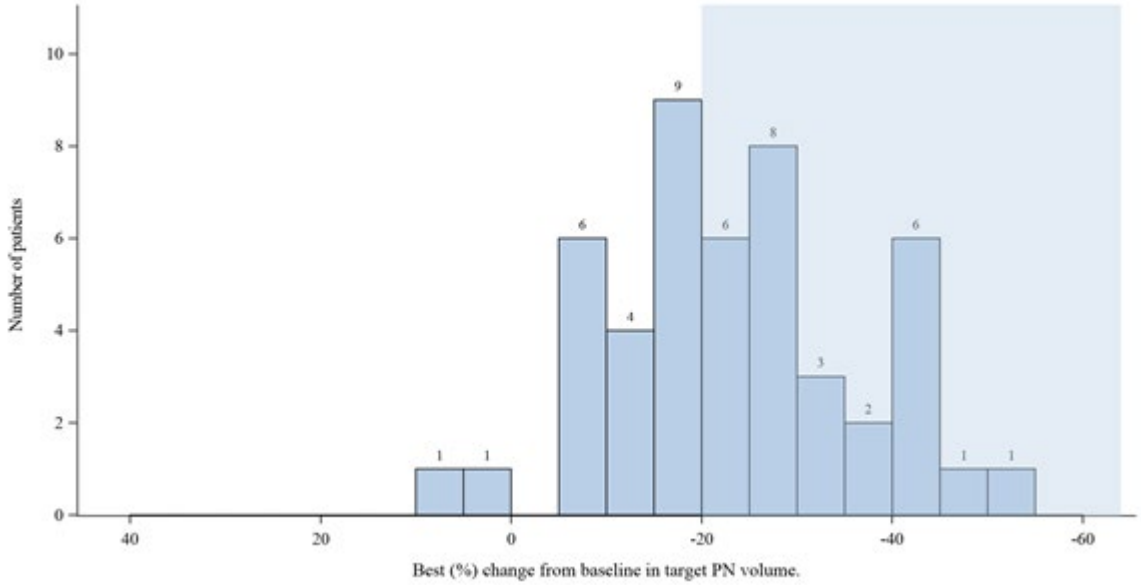
Best percentage change in target PN size is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. Bars not annotated with SN or N represent typical nodular PN. Includes a patient who only has partial volumes throughout the study.
FAS Full Analysis Set; PN Plexiform neurofibroma N Nodular PN; SN Solitary nodular PN; U Unconfirmed response.

Figure 24: SPRINT Phase II Stratum 1 (pivotal data): Best percentage change from baseline in target PN volume - ICR analysis - Waterfall plot (FAS)

NCI POB Central Analysis



First ICR Analysis



Best percentage change in target lesion size was the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. Grey background shows the best percentage change less than -20%.
REiNS (ICR) assessment.
The width of each histogram bar corresponds to a 5% PN volumetric change from baseline.
Includes a patientwho only had partial volumes throughout the study.
ICR = Independent central review; NCI = National Cancer Institute; PN = Plexiform neurofibroma; POB = Pediatric Oncology Branch; REiNS = Response Evaluation in Neurofibromatosis and Schwannomatosis.
Figure 25: Best Percentage Change From Baseline in Target PN Volume

–Duration of response

Based on the ICR assessment, using the same REiNS criteria as the NCI POB central analysis, of the 22 patients with confirmed PR, 7 patients subsequently had disease progression. Median DoR was 32.0 cycles (95% CI: 18.0, 32.0).

DoR - using NCI POB-based imaging assessments' actual dates

A sensitivity analysis using the actual dates of the volumetric MRI assessments (rather than DoR estimated in cycles used for the primary analysis) was performed to account for any delays or interruptions. The number (percentage) of patients remaining in response after 12 and 24 months was 27 (81.8%) and 6 (18.2%), respectively. When estimated using the Kaplan-Meier method, the probability of remaining in response after 12 and 24 months was 100% and 90.2%, respectively

Second ICR of Volumetric MRI Assessments of Target PN Only According to the REiNS Criteria

A retrospective sensitivity analysis of volumetric MRI assessments (target PN only) according to the REiNS criteria by a second ICR was performed .

This second ICR was performed according to the same methodology as the first ICR, i.e. methodology that is not fully in line with the PA recommendations. Although the reviewers were blinded to visit date and visit name, they were presented images of each patient in a sequential order.

Target PN Volume over time

A summary of the best percentage change from baseline statistics is presented in Table 38. Overall there was a reduction in target PN volume consistently detected by all reads (NCI POB, and first and second ICR reads).

Table 33: Best Percentage Change from Baseline in Target PN Growth During SPRINT Phase II Stratum 1 by NCI POB, First ICR, Second ICR and Average ICR

Read	Mean	StdDev	Min	Median	Max
NCI POB Central Analysis	-25.28	12.33	-54.5	-27.85	2.2
First ICR	-23.41	13.348	-53.7	-22.05	9.5
Second ICR	-22.58	13.093	-52.3	-19.60	4.6
Average ICR	-22.78	12.744	-53.0	-22.64	3.6

Best change in the PN volume is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction.
Based on target PN volumes from 48 patients who had post-baseline scans.
A negative value denotes a reduction in PN volume.
ICR = Independent central review; MRI = Magnetic resonance imaging; NCI = National Cancer Institute; PN = Plexiform neurofibroma(s); POB = Pediatric Oncology Branch; StdDev = Standard deviation.

ORR Based on ICR

Averages ICR ORR based on tumour responses were programmatically evaluated based on REiNS criteria using the average of the volumetric measurements by the two ICR reads at each scheduled MRI assessment.

Table 34: Confirmed ORR: First ICR, Second ICR and Average of two Different ICR Assessments (REiNS; Full Analysis Set, N = 50)

	Selumetinib 25 mg/m^2 BID (N = 50)		
	First ICR [a]	Second ICR	Average ICR [d]
Number (%) of patients with a response [b]	22 (44.0)	20 (40.0)	22 (44.0)
95% CI [c]	30.0, 58.7	26.4, 54.8	30.0, 58.7

[f] Based on ICR ORR analysis submitted in Day 0 MAA submission.

For PRs, response required consecutive confirmation within 3 to 6 months after the criteria for first response were met.
Calculated using the Clopper-Pearson exact method for binomial proportions.
ORR calculated from the average of the volumetric PN measurements by the 2 ICR reads.
ORR was defined as the number (percentage) of patients who received at least 1 dose of selumetinib and had at least 1 CR or confirmed PR.
BID = Twice daily; CI = Confidence interval; CR = Complete response; ICR = Independent central review; ORR = Objective response rate; PR = Partial response; REiNS = Response evaluation in neurofibromatosis and Schwannomatosis.

Concordance Analysis for BOR between First ICR and Second ICR

Concordance between the assessment of target PN BOR by first and second ICR Read, using REiNS criteria is summarised in Table 40:

Table 35: Concordance in Categories of BOR Between first ICR and second ICR (REiNS; Full Analysis Set, N = 50)

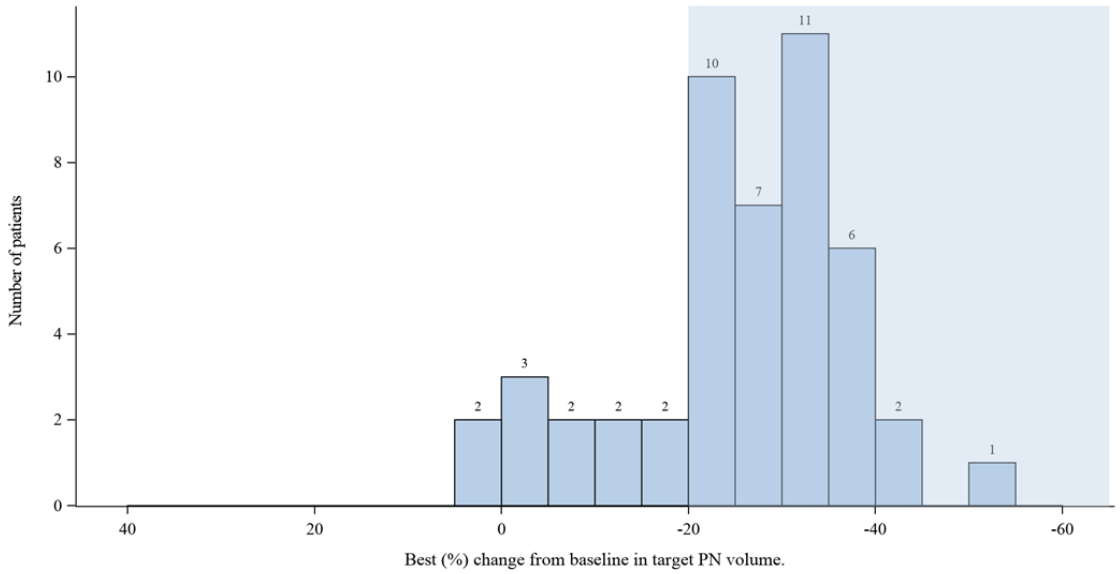
Best objective response per second ICR [b]	Best objective response per first ICR [a]						
	CR	Confirmed PR	Unconfirmed PR	SD	Progression	NE	Total
CR	**0**	0	0	0	0	0	0
Confirmed PR	0	**18 (36.0)**	1 (2.0)	1 (2.0)	0	0	20 (40.0)
Unconfirmed PR	0	0	**2 (4.0)**	1 (2.0)	0	0	3 (6.0)
SD	0	4 (8.0)	2 (4.0)	**19 (38.0)**	0	0	25 (50.0)
Progression	0	0	0	0	**0**	0	0
NE	0	0	0	0	0	**2 (4.0)**	2 (4.0)
Total	0	22 (44.0)	5 (10.0)	21 (42.0)	0	2 (4.0)	**50 (100)**

[g] First ICR tumour response assessments according to modified REiNS.
Second ICR tumour response assessments according to modified REiNS.
Numbers in bold indicate when BOR is the same for both first and second ICR.
The denominator used in the calculation of the percentages was the total overall sample size.
BOR = Best objective response; CR = Complete response; ICR = Independent central review; NE = Not evaluable; PR = Partial response; REiNS = Response evaluation in neurofibromatosis and Schwannomatosis; SD = Stable disease.

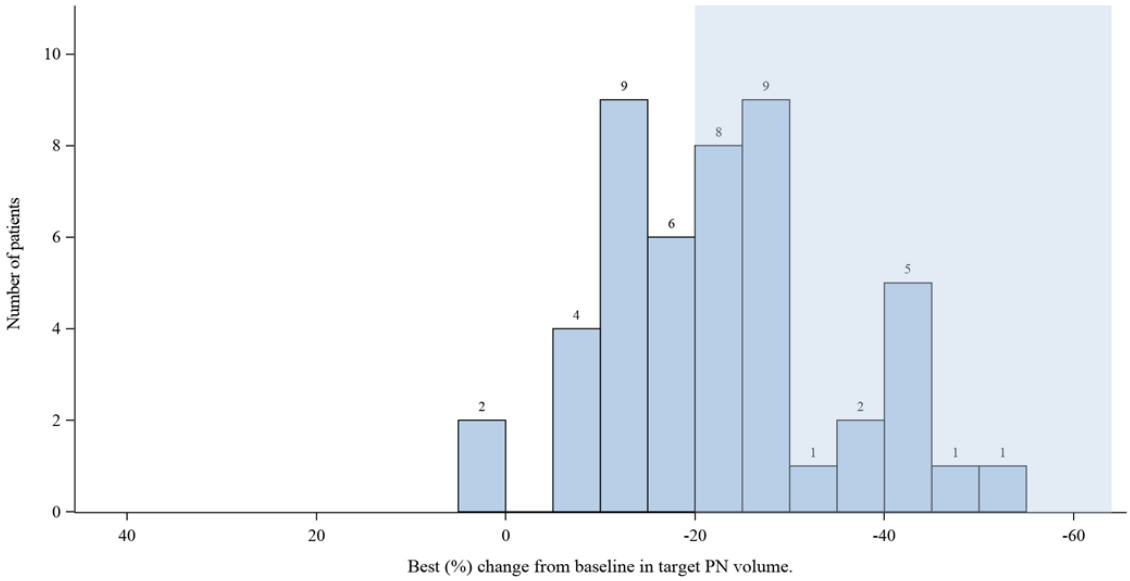
Concordance Analysis for BOR Between NCI POB Central Analysis and Average ICR

Histograms of best percentage change from baseline in target PN volume based on both the NCI POB central analysis and average ICR analyses are presented in Figure 26.

NCI POB assessment



ICR Average



Best percentage change in target lesion size is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. The width of each histogram bar corresponds to a 5% PN volumetric change from baseline.
Shaded background is for best percentage change less than -20%.
REiNS assessment.
ICR = Independent central review; NCI = National Cancer Institute; PN = Plexiform neurofibroma(s); POB = Pediatric Oncology Branch; REiNS = Response evaluation in neurofibromatosis and Schwannomatosis; PN = Plexiform neurofibroma(s).

Figure 26: Best Percentage Change From Baseline in Target PN Volume by NCI POB and ICR Average

The concordance between the NCI POB central analysis and average ICR and to first ICR is presented in Table 41 and Table 40.

Table 36 Concordance in Categories of BOR between NCI POB Analysis and Average ICR (REiNS; Full Analysis Set, N = 50) and to First ICR

Best objective response per average ICR [b] analysis	Best objective response per NCI POB [a] analysis						
	CR	Confirmed PR	Unconfirmed PR	SD	Progression	NE	Total
CR	**0**	0	0	0	0	0	0
Confirmed PR	0	**20 (40.0)** ***21 (42.0)***	2 (4.0) *1 (2.0)*	0	0	0	22 (44.0)
Unconfirmed PR	0	3 (6.0)	**0** ***1 (2.0)***	2 (4.0) *1 (2.0)*	0	0	5 (10.0)
SD	0	10 (20.0) *9 (18.0)*	2 (4.0)	**9 (18.0)** ***10 (20.0)***	0	0	21 (42.0)
Progression	0	0	0	0	**0**	0	0
NE	0	0	0	0	0	**2 (4.0)**	2 (4.0)
Total	0	33 (66.0)	4 (8.0)	11 (22.0)	0	2 (4.0)	**50 (100)**

[a] NCI POB tumour response assessments according to REiNS.
[b] Average ICR tumour response; programmatically assigned based on average of volumetric assessments performed by two different ICR according to REiNS.
Numbers in italics indicate the concordance between the NCI POB central analysis and first ICR analysis where different from the average ICR (Module 2.7.3, Table 18).
Numbers in bold indicate when BOR matches for both NCI POB and average ICR.
The denominator used in the calculation of the percentages was the number of patients in the Full Analysis Set.
BOR = Best overall response; CR = Complete response; ICR = Independent central review; NCI = National Cancer Institute; NE = Not evaluable; POB = Pediatric Oncology Branch; PR = Partial response; REiNS = Response evaluation in neurofibromatosis and Schwannomatosis; SD = Stable disease.

Concordance analysis

Concordance between assessment of target PN best objective response by NCI POB central analysis and ICR analysis is summarised in Table 42.

Table 37: Concordance in categories of best objective response between NCI POB central analysis and ICR analysis (FAS)

Objective response per ICR analysis	Objective response per NCI POB central analysis						
	Complete Response	Confirmed PR	Unconfirmed PR	Stable disease	Progression	Not evaluable	Total
Complete response	0	0	0	0	0	0	0
Confirmed PR	0	21 (42.0)	1 (2.0)	0	0	0	22 (44.0)
Unconfirmed PR	0	3 (6.0)	1 (2.0)	1 (2.0)	0	0	5 (10.0)
Stable disease	0	9 (18.0)	2 (4.0)	10 (20.0)	0	0	21 (42.0)
Progression	0	0	0	0	0	0	0
Not evaluable	0	0	0	0	0	2 (4.0)	2 (4.0)
Total	0	33 (66.0)	4 (8.0)	11 (22.0)	0	2 (4.0)	50 (100)

The denominator used in the calculation of the percentages was the number of patients in the Full Analysis Set.
CR Complete response; FAS Full Analysis Set; ICR Independent central review; NCI National Cancer Institute; POB Pediatric Oncology Branch; PR Partial response; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.

ORR Subgroup analysis by PN status at enrolment

The results of a subgroup analysis (per NCI POB central analysis) of ORR by PN status at enrolment was as follows: In the 21 patients who had progressive PN at enrolment the ORR was 61.9% (13/21; 95% CI: 38.4, 81.9), in the 15 patients with non-progressive PN at enrolment the ORR was 66.7% (10/15; 95% CI: 38.4, 88.2), and in the 14 patients classified as "*Unknown*" the ORR was 71.4% (10/14; 95% CI: 41.9, 91.6).

ORR Subgroup analysis by age at Study Entry

Table 47 shows that there was a numerically higher ORR in the youngest age group, which is in line with previous observations (Dombi et al 2020).

Table 38: Confirmed Objective Response Rate by Age at Baseline – SPRINT Phase I and Phase II Stratum 1 (NCI Analysis) Combined (Full Analysis Set)

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

[a] SPRINT Phase II Stratum 1: Response required consecutive confirmation within 3 to 6 months after the criteria for first response were met. SPRINT Phase I: Response required confirmation at least 4 weeks after the criteria for first response were met; Partial response = a decrease in the volume of the target PN by 20% or more compared with baseline.

[b] The CIs were calculated using Clopper-Pearson exact method for binomial proportions.

Objective response rate was defined as the number (%) of patients who received at least one dose of selumetinib and had at least one complete response or confirmed partial response occurring prior to study treatment discontinuation.

CI = Confidence interval; NCI = National Cancer Institute; PN = Plexiform neurofibroma(s).

Source: IEMT71b3

Impact of dose reductions and interruptions on tumour growth

In SPRINT Phase II Stratum 1, all 50 patients had at least 1 dose interruption. AEs leading to dose reduction of selumetinib were reported in 12 (24.0%) patients. Discontinuation of selumetinib due to AEs was observed in 6 (12.0%). Of the 12 patients who had at least 1 dose reduction due to an AE, 4 patients had a second dose reduction.

A graphical longitudinal analysis was performed to plot target PN growth rate in patients with 2 dose reductions (4/50 patients), patients with 1 dose reduction (8/50 patients) and patients with no dose reduction but with cumulative interruptions (consecutive or not) between 2 assessments of either more than 28 days (6/50 patients) or less than 28 days (32/50 patients).

Tumour volume increases have been observed in patients with 2 dose reductions or with a dose reduction in addition to prolonged interruptions.

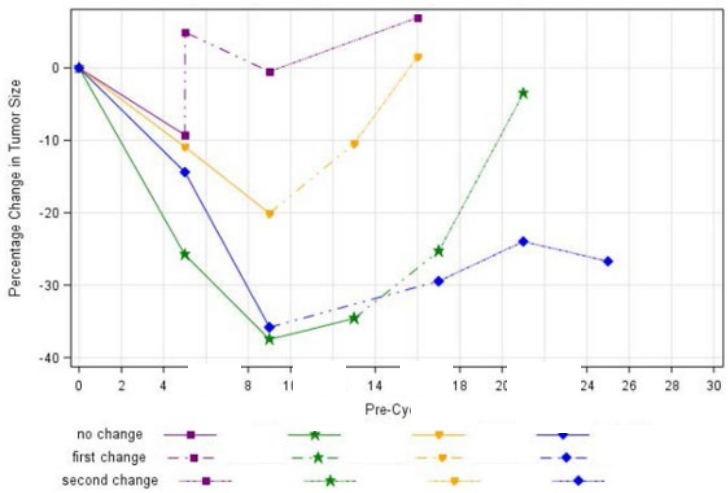


Figure 27: Target PN growth rate in patients who had 2 dose reductions (FAS)

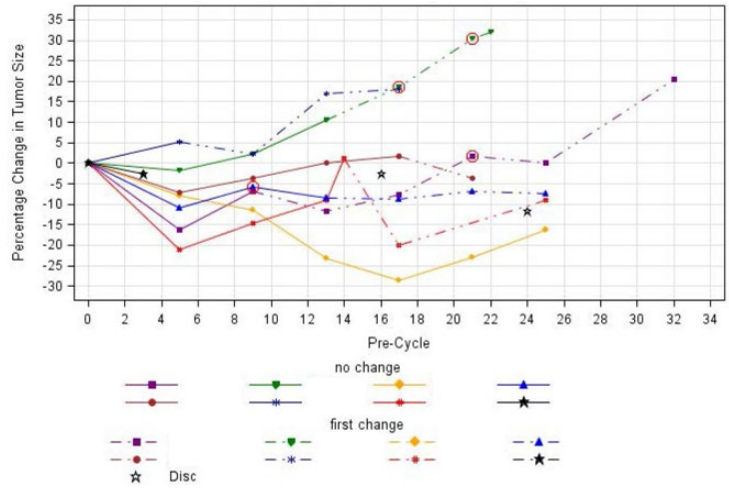


Figure 28: Target PN growth rate in patients with 1 dose reduction (FAS)

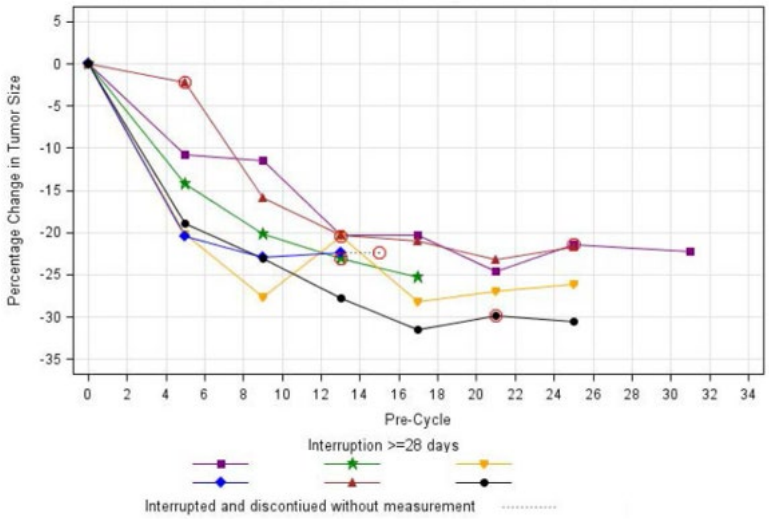


Figure 29: Target PN growth rate in patients with no change in dose and with cumulative interruptions more than 28 days between tumour assessments

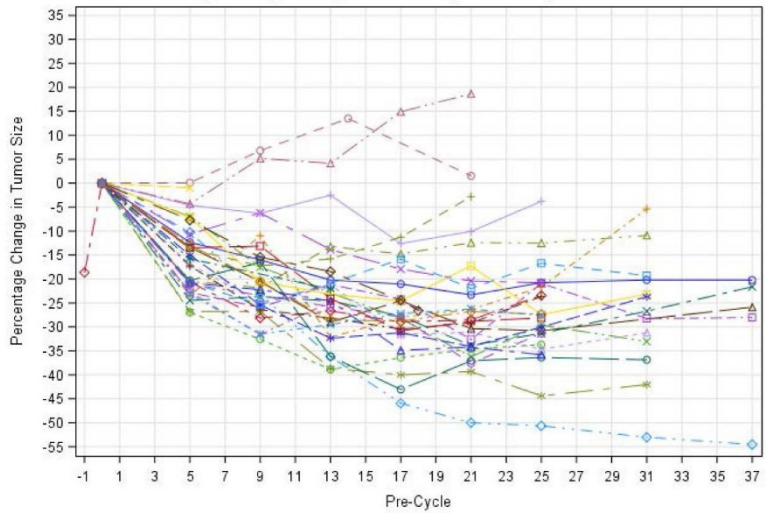


Figure 30: Target PN growth rate in patients with no change in dose and with cumulative interruptions less than 28 days between tumour assessments (FAS)

Supplementary post hoc analysis of ORR, DoR and PFS

Supplementary post hoc analyses of ORR, DoR and PFS were also presented, using all evaluable available volumetric MRI scans, regardless of schedule and regardless of treatment discontinuation, and using actual study day as opposed to number of cycles received.

ORR

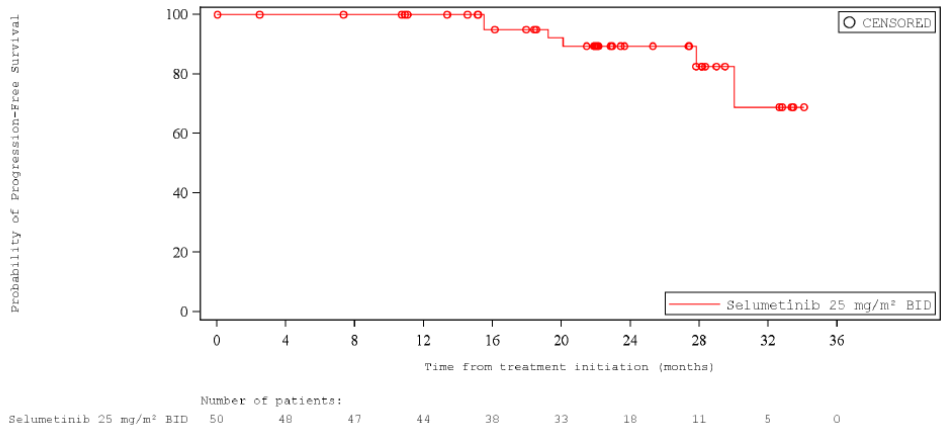
ORR by this analysis was 66.0% (33/50; 95% CI: 51.2, 78.8), i.e. the same as by the analysis including only the scheduled scans.

DoR

For DoR, the results of this analysis corresponded exactly to the results of the sensitivity analysis using actual dates (see above).

PFS

A KM plot showing PFS based on all available volumetric MRI scans is presented in Figure 31. According to this analysis, 6/50 (12.0%) patients progressed, i.e., 3 more patients than were found to have progressed using the PFS primary analytical method.



PFS is defined as the time from study treatment initiation until the date of objective disease progression or death (by any cause in the absence of progression). Patients not known to have progressed at the time of analysis are censored at the date of last evaluable on-treatment volumetric MRI assessment.
The values at the base of the figure indicate number of patients at risk. Dots represent censored observations.
PFS Progression-free survival.

Figure 31: Kaplan-Meier plot of PFS using all available volumetric MRI scans: NCI POB central analysis (FAS)

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 39: Summary of efficacy for trial SPRINT Phase II Stratum I

Title: Phase I/II Study of the Mitogen Activated Protein Kinase Kinase (MEK) 1 inhibitor selumetinib (AZD6244; HYD Sulfate) in children with Neurofibromatosis Type 1 (NF1) and inoperable Plexiform Neurofibromas (PN)		
Study identifier	Study Code D1532C00057 NCT Number NCT01362803 EudraCT Number 2016-000847-16	
Design	open-label, single-arm, multi-centre study	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	2 years not applicable not applicable

Hypothesis	A null hypothesis response rate of 15% and an alternative hypothesis response rate of 36%		
Treatments groups	Selumetinib (Full Analysis Set [**FAS**])		25 mg/m² administered orally BID continuously for 28-day cycles with no rest periods between cycles
Endpoints and definitions	Primary endpoint	Objective response rate (**ORR**)	Percentage of patients with complete response (CR defined as complete disappearance of target P) or confirmed partial response (PR; defined as PN decrease ≥20% compared with baseline (PR was considered unconfirmed at first detection and confirmed when observed again within 3 to 6 months)
	Secondary endpoint	Duration of response (**DoR**)	Time from the pre-cycle volumetric MRI assessment of the first documented response (subsequently confirmed) until the pre-cycle volumetric MRI assessment of documented progression on treatment or death in the absence of disease progression
	Secondary Endpoint	Progression-free survival (**PFS**)	Time from first volumetric MRI assessment to the date of documented progression or death in the absence of disease progression.
	Secondary Endpoint	Time to progression (**TTP**)	Time from study treatment initiation until pre-cycle volumetric MRI assessment of objective disease progression on treatment
	Secondary Endpoint	Pain evolution from baseline	Effect on pain using: NRS-11, Pain Interference Index (PII), Pain Medication Survey
	Secondary Endpoint	Motor PN	Effect on Motor PN using: strength, range of motion, PROMIS (mobility and upper extremity), grooved pegboard test, leg length evaluation
	Secondary Endpoint	Quality of Life	Health-related Quality of Life: PedsQL, QoL background form Physical functioning: 6-minute walk test (only in patients with lower extremity PN, cord compression or airway PN)
	Secondary Endpoint	Disfigurement	Photography (+/- video) evaluation
Database lock	Study ongoing (data cut-off date [DCO]: 29-Jun-2018)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS for all endpoints, unless indicated otherwise DCO 29-Jun-2018 Median follow-up (range): 24.0 cycles (0.0 to 36.0)			
Descriptive statistics and estimate variability	Treatment group	selumetinib		
	Number of subject	50		

	ORR Nbre of patient (%)	66%	95% CI 51.2,78.8
	Median **DoR** (months)	Not calculated (NC)	NC
	Median **PFS/TTP** (months)	Not calculated (NC)	NC
	Median**TTR** (months)	Not calculated (NC)	NC
	NRS-11 Cycle 13 (n=24)	Mean -2.07	95% CI: -2.84, -1.31

	PII Cycle 13	Median reduction Self-reported 0.67 Parent reported 1.50	 Range 0 to 5.5 Range 0 to 4.8
	PROMIS mobility	Mean reduction self-reported 1.75 Parent reported 2.75	95% CI: -0.70, 4.19 1.02, 4.48
	PROMIS Upper extremity	Mean reduction Self-reported 1.76 Parent reported 1.53	95% CI: -0.88, 4.39 -1.06, 4.12
Notes	A treatment cycle is 28 days		

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

External Control data

- NCI POB NF1 Natural History study

Design of Natural History study

The Natural History study is a prospective study in patients with NF1, which is sponsored and conducted by the NCI POB. This study serves as an umbrella protocol for NCI POB's clinical study programme and the scope of this study is broader than the data being presented for this application.

The Natural History study enrols both paediatric and adult patients aged ≤35 years old with a clinical diagnosis of NF1 or a confirmed NF1 mutation, patients are not required to have PN-related morbidity at enrolment. There is no upper age limit for patients previously enrolled on clinical studies at the NIH or for patients diagnosed with Malignant peripheral nerve sheath tumours (MPNST), or with clinical concern for MPNST, or with infrequent or unusual NF1-related manifestations. Patients must have an ECOG performance status ≤3. There are no restrictions in this study regarding prior treatment (e.g., surgery or radiation) or received investigational therapies (including selumetinib) within clinical studies including the SPRINT protocol. The Natural History study plans to enrol up to 250 patients, with evaluations for up to 10 years after the last patient is enrolled to allow analysis over a meaningful duration of time.

Enrolment started in 2008 and was ongoing at the DCO for this application.

Use as external control for SPRINT Phase II Stratum 1

The volumetric MRI analyses were performed by a central reviewer at the NCI POB. For patients with multiple PN in the NH study only 1 PN per patient was selected by NCI POB for analysis and only the volumetric MRI data of the same PN in each patient, which had been followed up for the longest period of time, not affected by surgery and prior to treatment with any MEK inhibitor, was selected to be included in the NH analysis.

NH study data were presented using 3 analysis sets:

- For the patients in the **full NH analysis set** (all ages and who have at least 2 volumetric MRI scans), the first volumetric MRI analysis was used as the baseline PN assessment. The final volumetric MRI assessment was considered to be the last volumetric MRI assessment or last volumetric MRI assessment prior to the first use of a MEK inhibitor including selumetinib.
- The **primary analysis set** used as an external control for SPRINT data **is the age-matched cohort**. This is a subset of the full NH analysis set including patients with at least 2 volumetric MRI scans where the first volumetric MRI scan done within the age range of 3 to 18 years was used as the baseline PN assessment for the NH study. The final volumetric MRI assessment was considered to

be the last volumetric MRI assessment or last volumetric MRI assessment prior to the first use of a MEK inhibitor including selumetinib.

- For the patients enrolled into the NH study who then enrolled into SPRINT Phase II Stratum 1, where there was volumetric MRI data of the same PN that was followed up during both studies (i.e. the **NH subset**), the first volumetric MRI analysis was used as the baseline PN assessment. The final volumetric MRI assessment was considered to be the last volumetric MRI assessment or last volumetric MRI assessment prior to the first use of a MEK inhibitor including selumetinib. Of note, for patients in the NH subset, the target PN followed in the overall NH analysis may be different from the target PN followed in the NH subset analysis. Two paediatric patients who participated in both studies were excluded from this dataset as different PN were followed in the NH study and SPRINT Phase II Stratum 1.

Analyses were presented based on the following time periods for all 3 analysis sets:

- All available follow-up (i.e., maximum of 17.7 years): From the first volumetric MRI assessment date up to the last available volumetric MRI assessment or last assessment date prior to the first use of a MEK inhibitor, including selumetinib.
- Aligned to maximum follow-up duration of SPRINT Phase II Stratum 1 (i.e., 2.8 years).

PN growth rates for the patients in the NH study and SPRINT Phase II stratum 1 were evaluated using 2 different methods: crude estimation and mixed models:

- For the NH study, crude PN growth rate was defined as the percent change in PN volume from the first to the last volumetric MRI assessment over the time period in years, where the time period was defined from the first to the last available volumetric MRI assessment or last volumetric MRI assessment date prior to the first use of a MEK inhibitor, including selumetinib. This estimate was also derived for the time period aligned to the maximum follow-up duration observed in SPRINT Phase II Stratum 1, i.e., 2.8 years.
- For SPRINT Phase II Stratum 1, crude PN growth rate was defined as the percent change in target PN volume from the baseline volumetric MRI to the last volumetric MRI assessment over the time period in years, where the time period was defined from the baseline volumetric MRI assessment date to the last evaluable assessment date up to data cut-off or treatment discontinuation (whichever occurred first).
- For the NH study, only for the full and age-matched analysis sets, a random coefficient mixed model was fitted to get adjusted estimates for growth rate. The model included percent change from baseline in PN volume as response, subject and time as a random effects and baseline age and baseline PN volume as fixed effects, using an unstructured covariance matrix. This model was repeated to include only data up to 2.8 years follow-up, to align with the maximum follow-up duration in SPRINT Phase II Stratum 1.
- For SPRINT Phase II stratum 1, a repeated measure mixed model was fitted. It included percent change from baseline in PN volume as response, subject and time (continuous) as random effects, baseline age and baseline PN volume as fixed effects and visit as a repeated measure, using a spatial power covariance matrix.

The adjusted mean was presented for each study and is the predicted percentage growth from baseline after 1 year for a patient of median age and target PN volume at baseline (based on the medians in SPRINT Phase II Stratum 1).

The following analyses/matching strategies were performed using the age-matched cohort:

1. Naïve comparison (without using propensity score);

2. Matched 1:1 (without replacement) with a robust variance;

3. Weighted using stabilised IPTW;

4. Weighted using IPTW with a robust variance; and

5. Matched 1:2 (with replacement) with a robust variance.

Median **PFS** with 95% CIs was calculated using a KM plot for the full NH analysis set and age-matched cohort. This analysis was also repeated for the time period aligned to maximum follow-up in SPRINT (i.e., 2.8 years). In the NH study, progression was defined as a ≥20% increase in PN volume compared with baseline and PFS was defined as the time from the first volumetric MRI assessment to the date of documented progression or death in the absence of disease progression.

Baseline data

Demographic and disease characteristics at baseline for the NH study and SPRINT Phase II Stratum 1 are summarised in

Table 45. At baseline, median age and baseline target PN volume were higher in SPRINT Phase II Stratum 1 than in the full NH cohort and the age-matched cohort, and unsurprisingly the NH subset.

The number of patients who (had) received a prior medical treatment for PN was 72 (64.9%) in the full NH cohort and 31 (62.0%) in SPRINT Phase II Stratum 1. In both the most common PN-directed medical treatment was pegylated interferon. During the course of the NH study, patients were able to remain on or start medical treatment for NF1-related manifestations; therefore, the given proportion includes medical treatments at baseline and during the study. In the NH study, the medications received were either investigational or were used off label. For patients who received a MEK inhibitor, such as selumetinib, during the NH study, data collected during the MEK inhibitor treatment period have been excluded from all analyses.

Table 40: Baseline demographic and disease characteristics: Natural History study (overall and age-matched cohorts) and SPRINT Phase II Stratum 1 (FAS)

		Natural History study		SPRINT Phase II Stratum 1 Selumetinib 25 mg/m² BID (N=50)	Natural History subset enrolled in SPRINT Phase II Stratum 1 (N=9)	
		Full NH cohort (N=111)	Age-matched cohort (N=92)		During Natural History	During SPRINT Phase II Stratum 1
Age, years[a]	Median (range)	8.4 (0.6-40.2)	7.8 (3.0-17.0)	10.2 (3.5-17.4)	6.2 (1.7-12.9)	12.7 (5.5-16.7)
Sex, n (%)	Male	69 (62.2)	56 (60.9)	30 (60.0)	5 (55.6)	5 (55.6)
	Female	42 (37.8)	36 (39.1)	20 (40.0)	4 (44.4)	4 (44.4)
Target PN location[b], n (%)	Trunk	43 (38.7)	36 (39.1)	5 (10.0)	-	-
	Trunk/extremity	21 (18.9)	17 (18.5)	12 (24.0)	-	-
	Head	13 (11.7)	13 (14.1)	9 (18.0)	-	-
	Neck/trunk	16 (14.4)	13 (14.1)	12 (24.0)	-	-
	Extremity	7 (6.3)	7 (7.6)	4 (8.0)	-	-
	Head/neck	5 (4.5)	5 (5.4)	8 (16.0)	-	-
	Whole body	6 (5.4)	1 (1.1)	0	-	-
Target PN volume[b] (mL)	Median (range)	357.00 (3.7-4895.0)	301.50 (3.7-4895.0)	487.50 (5.6-3820.0)	-	-

[a] Full NH cohort: Age at baseline volumetric MRI assessment of target PN; Age-matched cohort: Age at first volumetric MRI assessment, where the patient is 3 to 18 years; SPRINT Phase II Stratum 1: Age at informed consent.

[b] These data for the NH subset were provided, but not summarized.

The age-matched cohort includes patients who are aged 3 to 18 years and have at least one volumetric MRI within this age and at least one subsequent volumetric MRI.

BID Twice daily; FAS Full Analysis Set; NCI National Cancer Institute; MRI Magnetic resonance imaging; NF1 Neurofibromatosis type 1; PN Plexiform neurofibroma; POB Pediatric Oncology Branch; SD Standard deviation.

Data as of: 19 February 2019 (Imaging data) and 19 March 2019 (Subset data); DCO: 29 June 2018 (SPRINT Phase II Stratum 1).

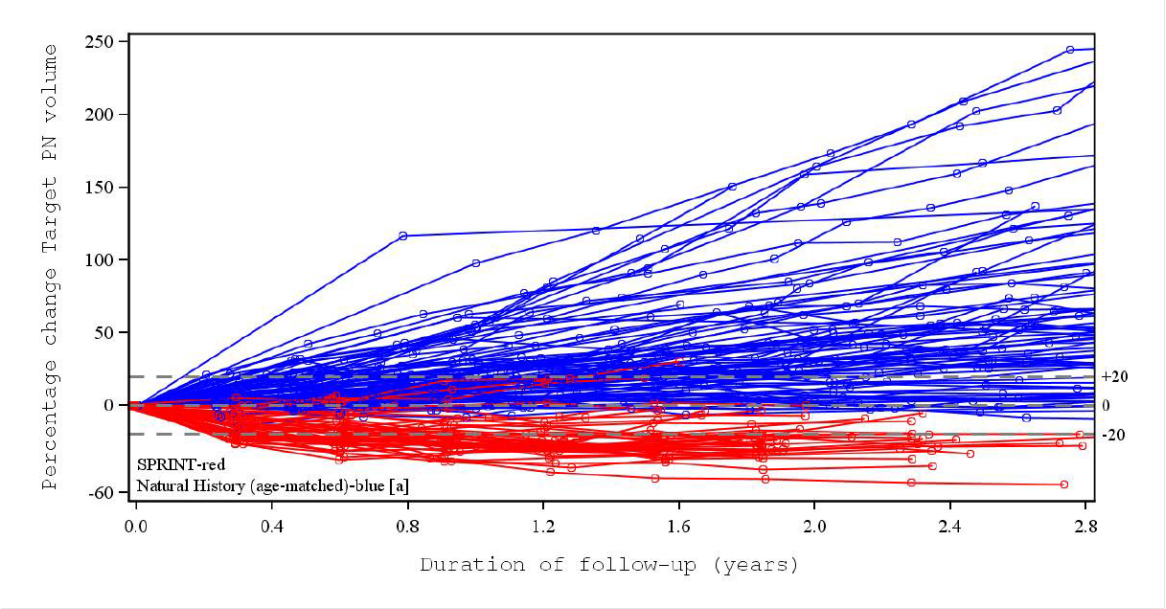
PN volume change

Age-matched cohort

In the Natural History age-matched cohort aligned to maximum follow-up duration in SPRINT Phase II Stratum 1, PN volume change from baseline ranged from -4.1% (shrinkage) per year to +147.9% (growth) per year. In contrast, in SPRINT Phase II Stratum 1, the PN volume change from baseline ranged from -27.3% (shrinkage) per year to +19.0% (growth) per year. The adjusted mean annual PN growth rate was +21.3% (95% CI: 15.9, 26.8) in the Natural History age-matched cohort, versus -16.9% (95% CI: -20.2, -13.5) per year in SPRINT Phase II Stratum 1.

Patients with at least 2 volumetric MRI assessments in each study (including baseline for SPRINT Phase II Stratum 1 are displayed in the figure below: 92 patients are presented in this plot for Natural History and 48 patients for SPRINT Phase II Stratum 1.

Note that the figure includes the 2 patients with only 1 volumetric MRI scan within the 2.8 years although these patients were not included in the growth analysis aligned to 2.8 years.



[a] Includes patients aged 3 to 18 years with at least 1 volumetric MRI within this age and 1 subsequent volumetric MRI.
Note: 92 patients are presented in this plot for Natural History and 48 patients for SPRINT Phase II Stratum 1.
Patients with at least 2 volumetric MRI assessments in each study (including baseline for SPRINT Phase II Stratum 1) are displayed in this figure.
Figure includes data up to maximum SPRINT follow-up duration.
PN Plexiform neurofibroma
Data cut-off: 15 Oct 2018.

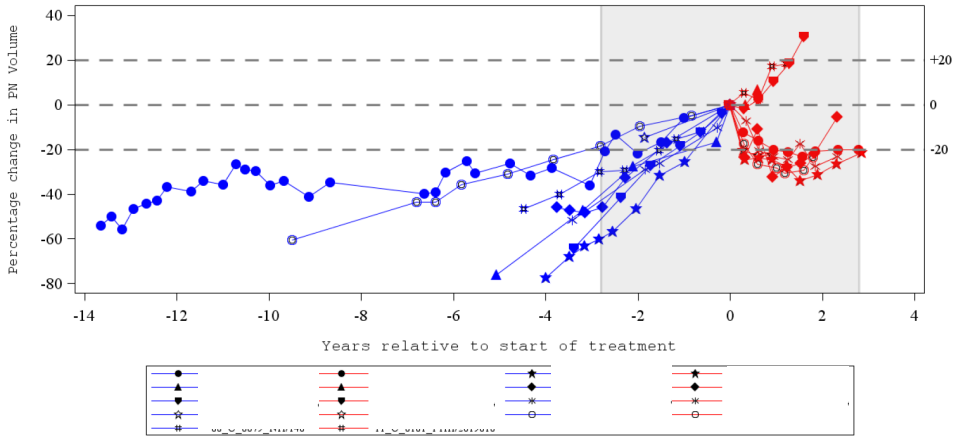
Figure 32: Percentage change in target PN volume, Natural History Study (age-matched; external control) and SPRINT Phase II Stratum 1 (pivotal data), individual patient data aligned to the maximum duration of SPRINT Phase II Stratum 1

NH subset

In total, 9 patients who enrolled into the NH study then enrolled into SPRINT Phase II Stratum 1, where there was volumetric MRI data of the same PN across both studies.

From baseline to final post-baseline volumetric MRI assessment, the median absolute and percentage change for the NH subset whilst in the NH study was 254.0 mL (range 51, 1353) and 118.4% (range 17, 343), respectively. For the same 9 patients whilst in SPRINT Phase II Stratum 1 this was -72.0 mL (range -742, +80) and -20.2% (range -24, +30), respectively.

Target PN growth data for individual patients, starting from the NH study through the last volumetric MRI assessment or last volumetric MRI assessment prior to the first use of a MEK inhibitor (including selumetinib) is presented in Figure 33. All 9 patients had varying rates of PN growth over the course of the NH study and, following selumetinib treatment, 6/9 patients had a reduction of at least 20% in their target PN (at first).



Patients with at least 2 volumetric MRI assessments in each study (including baseline for SPRINT Phase II Stratum 1) are displayed in this figure.
NH subset includes patients enrolled in the Natural History study and SPRINT Phase II Stratum 1 study with continuous PN volume data available (for the same PN) across both studies. PN followed in the overall Natural History analysis may differ from the PN followed in the NH subset analysis.
NH: Includes data up to the last volumetric MRI assessment or last volumetric MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib. SPRINT: Includes data up to the last evaluable assessment date up to data cut-off or treatment discontinuation.
Area of data collected before and after treatment start (with aligned follow-up) is highlighted.

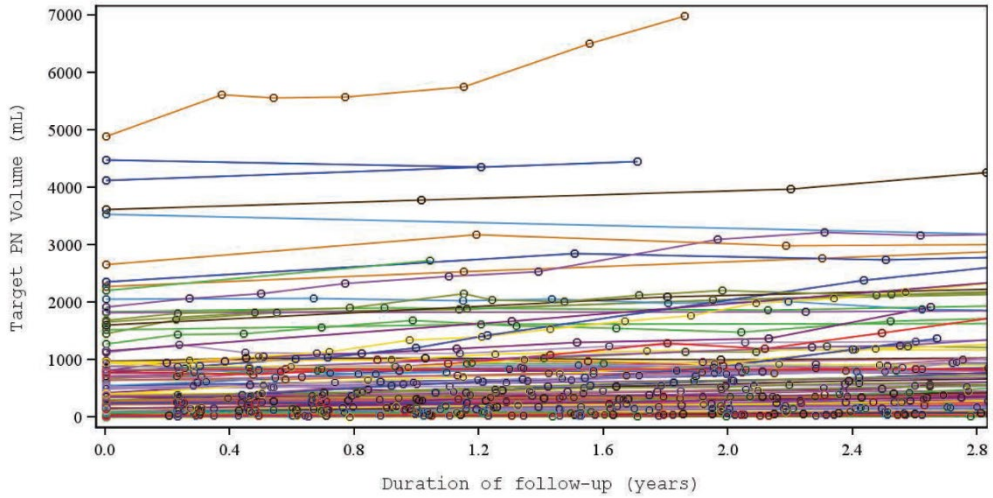
Figure 33: Percentage change in PN volume, individual patient data over time during Natural History study and SPRINT Phase II Stratum 1 (Natural History subset)

Full NH analysis set

From baseline to final post-baseline volumetric MRI assessment, the median absolute and percentage change for the full NH analysis set was +222.0 mL (range -370, +4725) and +73.4% (range -40, +1429), respectively. For SPRINT Phase II Stratum 1 this was -107.5 mL (range -964, +90) and -22.3% (range -55, +30), respectively. Four patients out of 111 had spontaneous shrinkage of ≥20% from baseline, which was achieved after 4-14 years on the NH study and at which time these four patients were aged 21-33 years. There was no spontaneous PN shrinkage of ≥20% within 1 year.

When aligned to maximum follow-up duration in SPRINT Phase II Stratum 1, the median PN volume change from baseline for the full NH analysis set was 17.8% per year (range -5.1% to 245.0%). In SPRINT Phase II Stratum 1, it was -10.2% (range -27.3% to 19.0%).

For the full NH analysis set, plots of absolute and percentage target PN volume change in individual patients over the maximum 17.7 years follow-up and over a follow-up of 2.8 years, i.e. aligned to the maximum FU duration of SPRINT Phase II Stratum 1, were provided. Of all these figures, only a spaghetti plot depicting each patient's target PN volume over 2.8 years is shown here (Figure 34).



111 patients are presented in this plot.
Patients with at least two MRI assessments are displayed in this figure.
NH = Natural History. PN = Plexiform neurofibroma.

Figure 34: Target PN volume, individual patient data aligned to maximum follow-up duration of SPRINT Phase II Stratum 1: Natural History study (full NH analysis set)

Progressive-free survival (PFS)

Definition

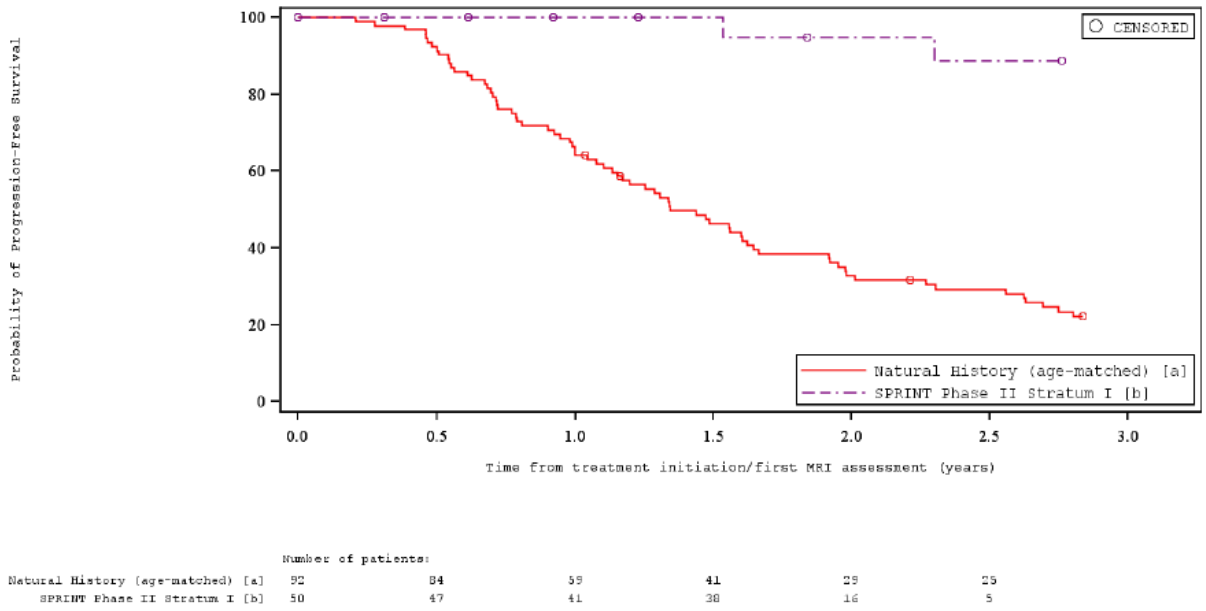
SRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression.

Natural History: PFS is defined as the time from first volumetric MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis were censored at the last available volumetric MRI assessment date or last volumetric MRI assessment date prior to the first use of a MEK inhibitor, including selumetinib.

Age-matched cohort

In the Natural History age-matched cohort aligned to maximum follow-up duration in SPRINT Phase II Stratum 1, the majority of patients had progressed (76.1%). Median PFS in the Natural History age-matched cohort was 1.3 years (95% CI 1.1, 1.6) with the probability of remaining without progressive disease after 2 years of 30.4% (95% CI 21.0, 40.3). The probability of remaining without progressive disease after 2 years on SPRINT Phase II Stratum 1 was 94.7% [95% CI: 80.6, 98.7]. The median PFS could not be estimated because most patients were still in response. Note that at 2 years, 29 patients were still followed in the Natural history group versus 16 in the SPRINT Phase II stratum 1 (and none in either group after 3 years).

Propensity analyses supported the primary analyses: PFS hazard ratio was 0.08 (95% CI: 0.02, 0.29) for the primary method (PSM 1:1) and was 0.09 for both PSM with replacement and IPTW methods.



a Includes patients who are aged 3 to 18 years with at least 1 volumetric MRI assessment within this age.
b Includes patients with a baseline volumetric MRI assessment.
Patients not known to have progressed or died at the time of analysis were censored at the last evaluable volumetric MRI assessment.
PFS in cycles converted to years: No. of cycles×28/365.25.
The values at the base of the figure indicate number of patients at risk. Dots represent censored observations.
DCO Data cut-off; MRI Magnetic resonance imaging; PFS Progression-free survival.

Figure 35: Kaplan-Meier plot of PFS in the Natural History age-matched cohort and SPRINT Phase II Stratum 1 aligned to maximum follow-up duration of SPRINT

When including all available follow-up, the number of PFS events (progression or death) in the NH study age-matched cohort was 80 (87.0%), i.e. 78 progressions (84.8%) and 2 deaths (2.2%). Median PFS was 1.3 years (95% CI: 1.1, 1.6). The probability of remaining without progression at 1 year was 64.1% (95% CI: 53.4, 73.0) and at 2 years 32.7% (95% CI: 23.3, 42.4).

Full NH analysis set

For the full NH analysis set the PFS data were similar to the PFS data for the age-matched cohort, both when aligned to the maximum follow-up duration of SPRINT Phase II Stratum 1, i.e. over a 2.8 year period, as well as with all available follow-up

- ***Placebo arm of tipifarnib Study 01-C-0222***

Study 01-C-0222 was sponsored by CTEP and coordinated by the NCI POB. This was a multi-centre, double-blinded, placebo-controlled, randomised, cross-over study of tipifarnib (R115777) in children and young adults (≥3 and ≤25 years) with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity (progressive ≥20% increase in PN volume, or ≥13% increase in 2-dimensional, or ≥6% increase in 1-dimensional measurement over last 2 consecutive volumetric MRI scans or within approximately 1 year prior to trial evaluation).

Patients were randomised to receive tipifarnib (200 mg/m² orally every 12 hours) or placebo (Phase A) and crossed over to the opposite treatment arm at the time of PN progression (Phase B). In each 28-day treatment cycle, study treatment was administered for 21 days followed by a 7-day rest period.

PN growth during the study was monitored using volumetric MRI. Volumetric MRI of up to 3 PNs was performed prior to the start of Cycles 1, 4, 7 and 10 and then after every 6 cycles (1 cycle=28 days). All volumetric MRIs were sent to the NCI POB for central analysis. A volumetric increase of ≥20% in at least 1 PN (any measurable lesion, regardless of whether it was target or non-target) compared with baseline was defined as progressive disease. In the tipifarnib study there was no differentiation between whether the lesion was a target or non-target PN in the assessment of progression.

Use as external control for SPRINT Phase II Stratum 1

The placebo arm from Phase A (first period of cross-over; N=29) of the study was used as an external control for patients from SPRINT Phase II Stratum 1 for TTP and PFS endpoints. Patients in the placebo arm of Phase A ranged in age from ≥3 to ≤18 years.

KM curves for PFS and TTP were produced separately for the placebo arm of the tipifarnib study during Phase A, all patients in SPRINT Phase II Stratum 1 and patients from SPRINT Phase II Stratum 1 with progressive PN at enrolment. Median PFS and TTP were calculated from the corresponding KM plot, with 95% CIs.

To enhance comparability between the placebo arm of the tipifarnib study and SPRINT Phase II Stratum 1, a further analysis that considered only the target PN lesions in the tipifarnib study (and not the non-target lesions) was implemented post hoc. Progression for the placebo arm of the tipifarnib study was programmatically derived by the Applicant considering only the target PN lesions and an additional PFS/TTP analysis was performed.

Table 41: Demographic and Other Subject Characteristics: Placebo Arm of Tipifarnib Study 01-C-0222 and SPRINT Phase II Stratum 1 (Progressive PN)

		Placebo arm of tipifarnib Study 01-C-0222 (N = 29)	SPRINT Phase II Stratum 1 (Progressive PN) Selumetinib 25 mg/m^2 BID (N = 21)
Age, years	Median (min, max)	8.2 (3-17.7)	8.10 (3.5-16.3)
Sex, n (%)	Male	14 (48.3)	15 (71.4)
	Female	15 (51.7)	6 (28.6)
ECOG performance score [a]	0	24	NA
	1	4	NA
	2	1	NA
Lansky performance status score [b]	n	NA	20
	Median (min, max)	NA	90 (80-90)
Karnofsky performance status score [b]	n	NA	1
	Median (min, max)	NA	80
Number of target PN [c]		31	21
Target PN volume, mL	Median (min, max)	316 (39.6-4896)	483.00 (5.6-1748.0)
Target PN location, n (%)	Neck/trunk	NA	3 (14.3)
	Neck/chest	9 (31.0)	NA
	Trunk/extremity	3 (10.3)	6 (28.6)
	Head	NA	4 (19.0)
	Face	3 (10.3)	NA
	Head/neck	4 (13.8)	3 (14.3)
	Trunk	NA	3 (14.3)
	Pelvis	6 (20.7)	NA
	Abdomen	2 (6.9)	NA
	Back	3 (10.3)	NA
	Extremity	1 (3.4)	2 (9.5)
Prior PN-directed medical treatments [f]	Yes	4 (13.8) [d]	13 (61.9) [e]
	No	25 (86.2)	8 (38.1)

[a] ECOG performance status was assessed in all patients. The ECOG performance status scores range from 0 to 5, with lower scores indicating better functioning.

[b] Lansky performance status was assessed in patients who were 16 years of age or younger and Karnofsky performance status was assessed in patients who were older than 16 years of age. Both the Lansky performance status and the Karnofsky performance status scores range from 10 to 100, with higher scores indicating better functioning.

[c] The PN chosen for volumetric MRI analysis to determine TTP/PFS.

[d] Three patients received methotrexate/vinblastine and one patient received pirfenidone.

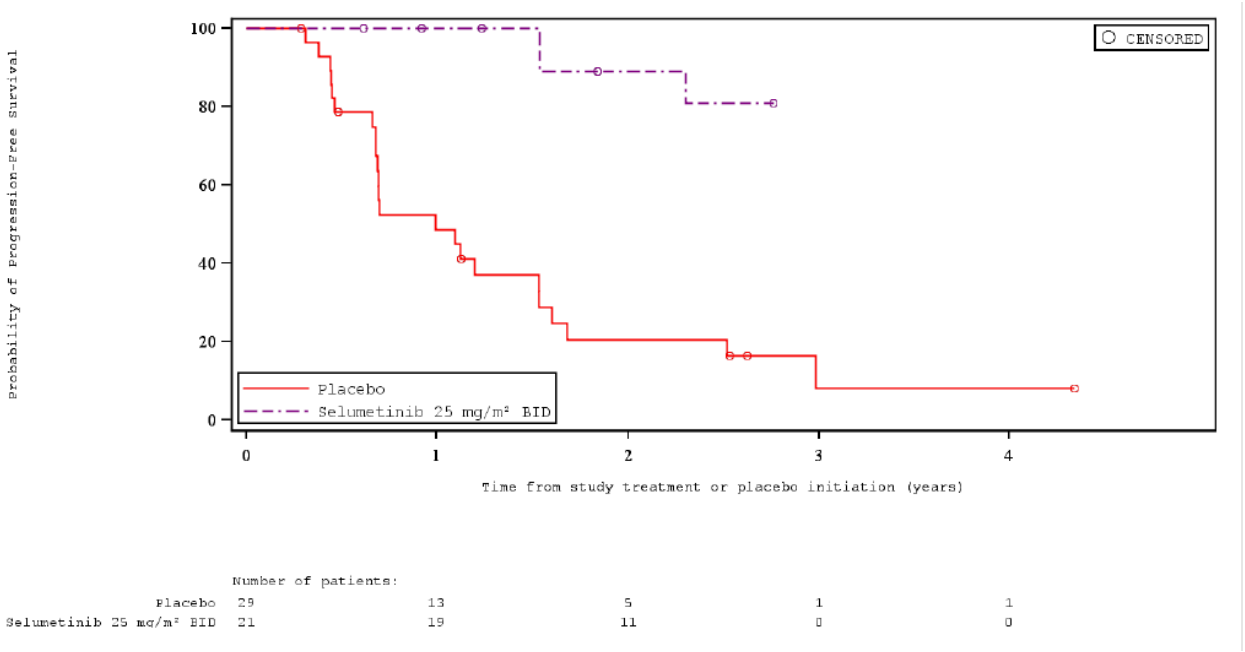
[e] The most common PN-directed medical treatments (> 20% of patients at the ATC level) were interferons.

[f] Medical treatments directed at other NF1 tumours may also be included.

ATC Anatomical Therapeutic Chemical; BID Twice daily; ECOG Eastern Cooperative Oncology Group; max Maximum; min Minimum; MRI Magnetic resonance imaging; NF1 Neurofibromatosis type 1; PFS Progression-free survival; PN Plexiform neurofibroma(s); TTP Time to progression.
Data as of: 15 February 2019 (placebo arm); DCO: 29 June 2018 (SPRINT Phase II Stratum 1).

Comparison of PFS (= TTP)

Using the subgroup of patients from SPRINT Phase II Stratum 1 with progressive PN at enrolment (N=21/50), the probability of remaining without progression at 2 years was higher (88.9% [95% CI: 62.4, 97.1]) than the placebo arm of tipifarnib Study 01-C-0222.



Includes patients with progressive disease in the 18 months prior to enrolment to SPRINT Phase II Stratum 1.
PFS is defined as the time from study treatment/placebo initiation until the pre-cycle/date of objective progression or death (by any cause in the absence of progression) for SPRINT Phase II Stratum 1/placebo arm of tipifarnib Study 01-C-0222, respectively.
Patients not known to have progressed or died at the time of analysis are censored at the last evaluable volumetric MRI assessment known to be non-progression.

Figure 36: Kaplan-Meier plot of PFS, placebo arm of tipifarnib Study 01-C-0222: Phase A and SPRINT Phase II Stratum 1 (Progressive PN)

An analysis of PFS/TTP in the placebo arm of the tipifarnib Study 01-C-0222 (Phase A), which considered only the target PN lesions, was performed to enhance comparability with the SPRINT study. In this analysis, of the 23 patients who progressed, 19 patients progressed based on target PNs only and 4 patients progressed due to non-target PNs only and were censored at the date of progression on non-target lesions, which corresponded to their last available MRI assessment.

The probability of remaining without progression at 2 years in the placebo arm of tipifarnib Study 01-C-0222, was 23.5% (95% CI: 8.8, 42.3). An early and maintained separation over time in favour of the patients from SPRINT Phase II Stratum 1 was observed when reviewing Kaplan-Meier curves of PFS.

Supportive study

See section 2.5.1. Dose response study.

Swallowability of Selumetinib 10 mg and 25 mg Hard Capsules

Selumetinib is formulated as a size 4 capsule measuring approximately 14 mm in length x 5 mm in width. The capsules cannot be crushed or broken and therefore the ability to swallow the capsules whole was an entry requirement for the SPRINT study. Training to swallow capsules was provided to those patients who needed it. Patients who were identified as having difficulty in swallowing the selumetinib capsule practiced with different surrogates i.e. hard candy of appropriate size (11.8 mm in length and 7 mm in width and/or 10.4 mm in diameter).

Of 74 patients enrolled in both SPRINT Phase I and Phase II Stratum 1, 46 patients were <12 years. Of these 10 required training. After training all 10 patients successfully showed their ability to swallow the capsules and they were subsequently recruited in the studies.

2.5.3. Discussion on clinical efficacy

The application is based on a single open-label, single arm, multi-centre phase I/II study developed by investigators at the National Cancer Institute (NCI), and coordinated by the NCI Paediatric Oncology Branch. The Applicant reviewed the protocol and provided selumetinib for the trial.

Additionally, the Applicant used as external control:

- Data from a Natural History non interventional prospective study conducted by the NCI POB.

- Data from patients included in the placebo arm of a tipifarnib randomised placebo controlled in children and young adults with NF1 and progressive PN.

SPRINT phase I was a multicentre, open-label, single arm, dose escalation study conducted in children with NF1 and inoperable PN designed to assess the safety of selumetinib and to identify the recommended phase II dose. There was no primary efficacy endpoint for this study. The key secondary objective was the percentage PN volume change, calculated from measurements taken using volumetric MRI analysis. Partial response (defined as target PN volume decrease ≥20% from baseline for ≥4 weeks) was observed in 66.7 % patients, 8.3% patients had an unconfirmed partial response and 20.8% a stable disease.

Initially, the doses to be tested ranged from 20 mg/m² BID (corresponding to 50 % of the fixed adult dose in cancer) to 50 mg/m² BID by steps of 10 mg. Two doses were tested 20 and 30 mg/m². However, following the publication of a trial (Banerjee et al. 2017) conducted concurrently by the Pediatric Brain Tumor Consortium in low-grade selumetinib-treated glioma in which the maximum tolerated dose was determined to be 25 mg/m² the trial was amended to evaluate this additional dose level and 6 patients were treated with this dose. On the basis of the available data, the 25 mg/m² dose was chosen as Recommended Phase II dose. When compared to 20 mg/m², efficacy results supported this choice.

Design and conduct of clinical studies

SPRINT Phase II (pivotal study) is an open label, non-controlled, single arm, multi-center study to assess efficacy and safety of selumetinib in children (aged 2 to 18 years old) with NF1 and PN could not be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN. Patients were enrolled in one of the 2 strata based on the presence or not of PN-related morbidity; Stratum 1: PN-related morbidity present at enrolment; stratum 2: no morbidity present at enrolment but potential for PN-related morbidity.

The inclusion was not limited to patients with progressive PN. The eligibility criteria are in general considered acceptable.

Due to the absence of approved medical treatment and the severity of the condition, the Applicant considered unethical to conduct a placebo-controlled study and that it was appropriate to conduct a single-arm open label study. However, and as was noted at follow-up Protocol Assistance (PA), relatively large-scale placebo-controlled studies in children with NF1 do appear in principle feasible (e.g. Payne et al. 2016 [n=146]). The choice to perform a single-arm study can be understood, but this has implications for the overall strength of evidence. Because of the lack of a comparator in the

pivotal study, a comparison with external controls, i.e. the tipifarnib study and the NH study, was provided to contextualise and help interpreting the results obtained with selumetinib.

Selumetinib is available as capsules (10 and 25 mg). All patients received 25 mg/m² BID orally with a maximum of 50 mg/m² BID. The dose was calculated according to the body surface of the child which evolves with growth and it was not possible to precisely adjust the dose according to the weight and height evolution in the absence of a suitable pharmaceutical form as the accuracy of the dose could not be less than 5 mg to 10 mg. Furthermore patients with a BSA <0.55 m² (dosage < 10 mg BID) could not be included and the dose had to be rounded to the nearest 5 or 10 mg. However, exposure – response analyses of SPRINT Phase I and Phase II (Stratum 1), suggest that higher exposures might be more beneficial.

Selumetinib is formulated as a size 4 capsule measuring approximately 14 mm in length x 5 mm in width. The capsules cannot be crushed or broken. In both parts of the study, only patients able to swallow capsules were included. After training, all patients in the pivotal study were able to swallow the capsules, however given limited number of patients these data are not considered sufficient to conclude that the product is age-appropriate in general. In addition, the capsules must be taken on an empty stomach 1 hour before or 2 hours after meal and with water only, which can pose a problem of acceptability and compliance for the youngest children.

The Applicant is currently developing an age-appropriate formulation more suitable for young children as reflected in the paediatric investigation plan and plan to submit a MAA line extension by 2024. The future selumetinib formulation might also provide better dose flexibility. The MAH should update the CHMP regarding the development of the new formulation in the context of the annual renewals.

The primary endpoint was defined as the percentage of patients with complete response or confirmed partial response (PR), with PR defined as target Plexiform Neurofibroma (PN) decrease ≥20% compared to baseline. Responses were considered confirmed if the PR was maintained at the subsequent MRI scan within 3 to 6 months after first response. Responses were assessed by NCI POB central analysis using 3D-volumetric MRI according to REiNS recommendations for imaging tumour response in neurofibromatosis clinical trials. Assessment was performed by a single reader which is considered subjective. It was therefore recommended during protocol assistance that the primary outcome was assessed by an average of ≥2 readers, who are independent and blinded for patient exposition and time point, and that sequential presentation of images from the same patient is avoided (via random presentation). Since a discrepancy between the investigator-based ORR and the first Independent Review-based ORR was observed (NCI-POB ORR of 66.0% and the ICR ORR of 44.0%), a retrospective sensitivity analysis of volumetric MRI assessments (target PN only) according to the REiNS criteria by a second ICR was performed. However, this second ICR was performed according to the same methodology as the first ICR, i.e. methodology that was not fully in line with the protocol assistance recommendations. Although the reviewers were blinded to visit date and visit name, they were presented images of each patient in a sequential order.

The secondary endpoints, clinical outcomes assessment (COAs) covered a wide range of clinical endpoints such as pain intensity (NRS-11), pain interference (PII), motor function (strength, range of motion, 6-minute walk test, PROMIS), airway function (FEV, Apnoea-Hypopnoea), bowel and bladder function, disfigurement, vision function, and quality of life (PedSQL).

In this setting, clinical outcome assessments are considered critical to demonstrate the clinical relevance of the observed tumour reduction. However, due to the open-label design, the lack of a comparator treatment arm and the small sample size, the interpretability of the clinical outcome endpoints is challenging. It is, however, agreed that symptoms and impact may vary based on the location and extent of PNs, and thus the use of multiple COAs can be understood. Many of the COAs applied to subsets of the study population only due to PN-specific morbidity and age-based restrictions.

Also, not all COAs used in the pivotal study were validated for, or reliable measures specific to the target NF1 population with symptomatic, inoperable PN. Therefore, the applied clinically meaningful thresholds (CMTs) are disputable. The NRS-11, PII and PROMIS instruments are recommended by the REiNS International Collaboration for the assessment of pain and physical functioning in NF clinical trials. These PRO instruments were applied in the study to age categories that differ only slightly from those recommended by the REiNS International Collaboration (see PN-associated clinical symptoms). This is acceptable for these secondary endpoints that are not regarded key. The results of all other COAs (airway function (FEV, Apnoea-Hypopnoea), bowel and bladder function, vision function, 6MWT), however, are thus of uncertain value.

The secondary endpoints DoR, PFS, TTP, and TTR are similarly, to the primary endpoint ORR, based on the NCI POB central analysis of PN volume and the changes in PN volume over time. These secondary endpoints are thus liable to the same (possible) subjectivity.

Efficacy data and additional analyses

The pivotal study included 50 patients, aged from 3.5 to 17.4 years (median 10.2 y; mean 10.3 y) at enrolment. Male represented 60% of the population. White subjects (84%) were the most presented patients.

At baseline, 78% of the patients had prior disease-related treatment. Prior medication were taken by 62 % of the patients and 56 % had prior surgery. As per investigator assessment, pain related to the target PN was present in half of the patients (52%).

The Objective Response Rate, based on NCI POB analysis was 66.0% (95% IC 51.2, 78.8). No patients had a complete response, 33 (66.0%) patients had a confirmed PR (volume decrease ≥ 20% confirmed within 3 to 6 months after first response), 4 (8.0%) had an unconfirmed PR and 11 (22%) had stable disease (volume change < 20%). No patients had a progression and 2 patients did not participate to this evaluation due to the absence of post baseline MRI scan.

Most responders (27/33 = 81.8%) maintained 20% shrinkage from baseline during the study (median follow up 24 cycles).

According to a sensitivity analysis by first ICR, an ORR of 44% was observed. No patient had a best objective response of progressive disease, 5 (10.0%) patients had an unconfirmed PR and 21 (42.0%) patients had stable disease. In line with the drop in ORR, the median best percentage change from baseline in target PN volume dropped to -22.05%.

The results of the second ICR showed that the trajectories of PN growth were largely in the same direction. Furthermore, there appeared to be considerable agreement between both ICR reads, and reasonable agreement between these and the NCI POB read. The second ICR ORR was 40% and the average ICR ORR was 44.0%.

Median duration of response was not reached as at DCO, only 2 of the 33 responders progressed. However, as by definition the response for each patient required confirmation within 3 to 6 months after the criterion for the first response was met, there is a guarantee-time bias introduced into the follow-up times (i.e. any patient who had an increase in tumour size before the second assessment would not be included in the subset of patients by definition). Median DoR is thus quite long compared to the 3-to-6-month guarantee-time bias. DoR sensitivity analysis confirmed the results of the primary analysis.

Median PFS was not reached as at DCO only 3 of the 33 responders progressed. Because no patient died during the study, the TTP results were identical to the PFS results.

There is little, and thus no robust data concerning the evolution of the tumour in case of discontinuation of selumetinib, and consequently a rationale for continuing therapy once the decrease in tumour volume has stabilized, has not been established.

The median TTR of 8 cycles (~8 months) is considered quite lengthy and, in the published article on the pivotal study, it is stated that the median time to *best* response was 16 cycles (Gross et al. 2020), i.e. twice as long. Considering the limited data and that some patients achieved a late response, a strict recommendation on the need to re-evaluate the interest of continuing treatment in the event of absence of response is not considered appropriate at this stage. The proposed recommendation in section 4.2 of the SmPC that treatment with Koselugo should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity is acceptable.

Concerning the pain linked to the target tumour, the NRS-11 instrument was used in patients aged ≥8 years. Moreover, baseline and pre-Cycle 13 data was available for less than half of the patients aged ≥8 years. A 'clinically meaningful' improvement was observed in half of these, i.e. approximately one in four patients of the FAS. An evaluation of the correlation between the reduction of the tumour and the clinical effect was carried out by applying the correlation coefficients of Spearman. In the 14 patients with a pain threshold ≥ 2 with baseline, there was a tendency to a positive correlation between the clinical improvement is the reduction of the tumour (r = 0.13).

The influence of pain on daily functioning showed some improvement in the score mainly supported by the scores reported by the parents. The correlation between shrinking tumour and PII was weak. Effect on tumour reported pain and global pain was also assessed by the GIC, individually some improvement was observed.

The effect on motility was assessed using self-PROMIS, and parent reported PROMIS score. A positive trend was reported as rated by parents but not for self-evaluation. At individual level, some patients showed a meaningful improvement but most of the patients showed no change. The correlation was moderate for self-reported score and weak for parent reported score regarding upper extremity score.

At baseline, disfigurement was the most common morbidity (44/50 patients 88%). It was captured by standardised photography and there was no formally planned method evaluating changes. It was only evaluated at a patient level and difficult to assess through the data provided.

The effect on quality of life was assessed through the PedsQL. There was a positive trend on the parent-reported data which was less apparent on the self-reported data. However, the open-label trial design limits interpretability those endpoints as patient's and parent's knowledge of treatment assignment may lead to an overestimation of treatment effect.

Overall, the figures show a trend towards an improvement in some treated patients, even if there is no statistical correlation between the decrease in the tumour and any clinical improvement at a population level, although some improvement in some clinical outcomes has been observed at an individual level.

In order to try to highlight a **link between the evolution of the tumour and the clinical outcomes**, the Applicant produced a table summarizing for each patient the clinical data at baseline (age, number of tumours, location of the target tumour, morbidities), the overall response, the rate of evolution of the volume of the tumour, the clinical responses observed, the evolution of the disfigurement as well as the treatment discontinuations and modifications dose (data not shown). However, the Investigator's assessment and the Applicant's summary of benefit are post-hoc and therefore likely biased in this open-label, single-arm study.

It is very plausible and has been shown that larger PNs cause more symptoms/morbidity (Nguyen et al. 2011) and/or that increases in PN volume are associated with increased symptoms/morbidity (Gross et

al. 2018). Therefore, the reverse could be considered equally plausible, i.e. that decreases in PN volume are associated with decreased symptoms/morbidity.

Overall, the individual improvement, confirmed by investigator's assessment associated with a durable reduction in tumour volume should be considered relevant in the context of a seriously debilitating rare disease and a high unmet medical need.

- ***Supportive data***

In addition to the SPRINT Phase II stratum 1 study, data from the Natural History study and the placebo arm of tipifarnib study were used as external control.

In the tipifarnib study only patients with progressive PNs were enrolled, whereas in the pivotal study patients were enrolled regardless of PN status at baseline. Median target PN volume was over 1.5 times higher in SPRINT Phase II Stratum 1 when compared to the tipifarnib study. In the scientific literature, it has been observed that larger PNs are associated with slower growth. Notwithstanding the differences in study design and patient population, the difference in PFS/TTP between the tipifarnib study and SPRINT Phase II Stratum 1 (progressive PN only) is clearly apparent from the KM curves.

The NH study had a non-interventional/observational study design and its eligibility criteria allowed for a far broader patient population to be enrolled than in SPRINT Phase II Stratum 1.

Median age was ~2 years higher and median target PN volume was ~1.5 times higher in SPRINT Phase II Stratum 1 when compared to the NH study full analysis set and age-matched cohort. For the vast majority of PNs in the NH study *age-matched cohort* the natural course seems to be to grow or at best stay stable over time. The median **PN growth rate** observed in the NH study age-matched cohort (15.1%/year to 21.3%/year) appears to be at the high end of what has been described in literature. In some patients, spontaneous shrinkage of the target PN was observed, but there was never a >20% change in PN volume from baseline or a decrease of ≥20% within 1 year. These observations are also in line with the scientific literature in which spontaneous shrinkage of PNs is described, but never exceeding -20%/year. The negative median growth rate (i.e. a decrease in volume) observed in the pivotal study compares favourably. The difference in **PFS/TTP** between the NH study age-matched cohort and the pivotal study is clearly apparent from the KM curves. The results of the *full NH analysis set* were similar to the results of the age-matched cohort, both for PN growth rate as well as for PFS.

While a beneficial effect on PFS is observed, the exact magnitude of this effect remains unknown.

Both external controls could provide some useful context data, however considering the heterogeneity of the baseline populations (age, disease progression, tumour volume) and the possible bias, it is difficult to carry out relevant comparative analyses between these 2 external controls and the pivotal study.

Supportive data from SPRINT Phase I were also presented. All efficacy results were similar to those of the pivotal study. It is noted that in SPRINT Phase I the definition/classification of response was not according to the REiNS criteria. The responses appeared quite durable. No dose-response relationship was apparent in the Waterfall plot of best percentage change from baseline in target PN volume.

Additional expert consultation

Upon request from the CHMP, an ad hoc expert group meeting (AHEG) was convened on 9 February 2021. The AHEG answers to the CHMP questions on efficacy aspects are as follows:

1. **To what extent does a response as measured by the REINS response definition (Dombi et al. 2013) represent patient benefit per se, and to what extent would support by results from clinical outcome assessments (COAs) be required?**

It was agreed that response as measured by REiNS criteria is a measure of activity that can be attributed to selumetinib. It was however not considered sufficient to conclude on patient benefit per se. However, it is acknowledged that the size of the tumour has direct implications on the symptoms and manifestations of neurofibromatosis type 1 (NF1) plexiform neurofibromas (PN) and a reduction in tumour size is therefore a critical outcome of the treatment. The responses have to be considered in the context of improved clinical outcomes that would vary depending on patients given the heterogeneity of the disease manifestations. In general, a good correlation is expected between response and duration of response, and improvement in clinical outcomes. Indeed, an association was observed between REiNS response and investigator-assessed clinical benefit.

2. **What, if any, clinical outcomes support clinical efficacy?**

It was agreed that the following clinical outcomes (not an exhaustive list) are of relevance in this condition: QoL, pain intensity, vision scale, motor scales, disfigurement. An effect on these clinical outcomes combined with a reduction of the tumour size would support efficacy of selumetinib. Although clinical outcomes improvements at a trial level were not observed for these endpoints, individual benefits were observed in a number of patients (pain intensity, motor function) and confirmed by investigators' assessments.

3. **Can the efficacy of selumetinib for the intended use be considered established based on the results from the pivotal study?**

The efficacy of selumetinib in patients with NF1 PN is considered established for the duration of follow-up (about 2 years median) as investigated in the pivotal trial. This is based on the expectation that response and the long duration of response observed will be associated in many patients with improvement in clinical outcomes. This assumption is considered well-justified on the basis of the expected effects of durable reductions in tumour volume and the individual patient benefits observed in the trial. Lack of an overall trial-level effect on the pre-specified clinical outcomes has to be considered in the context of improved clinical outcomes that would vary depending on patients given the heterogeneity of the disease manifestations. In conclusion, based on plausible assumptions and a number of reported individual benefits (pain intensity, motor function) as confirmed by investigators' assessments, efficacy is considered established.

There are however several uncertainties related to the uncontrolled nature of the study design and the fact that the impact of selumetinib on the natural course of the disease and long terms safety cannot be assessed. Both long term efficacy and safety will have to be carefully monitored in the post-marketing phase to address these uncertainties.

The AHEG also expressed concerns regarding the lack of guidance on treatment duration given the uncertainties on the benefit and harms of long-term treatment. Furthermore, lack of a suitable oral formulation will restrict use in some patients.

The lack of information regarding potential mechanisms of primary and secondary resistance were highlighted.

The AHEG also strongly recommended that prescription of selumetinib is restricted to physicians who are knowledgeable about plexiform neurofibromas.

Additional efficacy data needed in the context of a conditional MA

In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above, beyond the duration of the follow-up (about 2 years), the applicant will submit:

- Efficacy and safety data from the pivotal SPRINT Phase II Stratum 1 with longer follow-up. At the original DCO (29-Jun-2018) the median duration of selumetinib treatment in SPRINT Phase II Stratum 1 was 2.2 years (range 0.1 to 2.9 years). A second (unplanned) DCO on 31-Mar-2021 will provide 2 years and 9 months of further data. This would more than double the median follow-up.

- Supportive efficacy and safety data from SPRINT Phase I with longer follow-up. At the original DCO (29-Jun-2018) the median duration of selumetinib treatment in SPRINT Phase I was 4.4 years (range 0.4 to 5.9 years). A second DCO on 27-Feb-2021 will provide 2 years 8 months of further data. This would thus extend the total follow-up to 6-7 years.

2.5.4. Conclusions on the clinical efficacy

In the single-arm pivotal study SPRINT Phase II Stratum 1, 66% of the patient were responders by NCI POB central analysis and the median best percentage change from baseline in target PN volume was -27.85%. ORR appeared independent from PN status at enrolment and the responses appeared durable.

It is agreed that a response as measured by the REINS response definition (Dombi et al. 2013) represents patient benefit *per se.* The natural course of PNs is growth or at best stable over time, and any objective response observed in the pivotal study can in principle be attributed to selumetinib treatment.

The efficacy data package is limited, as the pivotal efficacy data are from a single Phase II study with only 50 patients.

The comparison to the external controls, i.e. the tipifarnib study and the NH study, is merely of a descriptive nature and hampered by differences between the pivotal study and these studies, regarding e.g. eligibility criteria and baseline demographic and disease characteristics.

ICR analyses of the imaging data from the pivotal study were performed showing ORRs of 40-44%. While the exact effect size of selumetinib treatment on PN volume/growth rate remains unknown, it is however assumed that a 'true' ORR (effect size) could be expected in the range of 40.0-66.0%, albeit with CIs extending from 26.4% to 78.8%. Supportive data from another 24 patients in SPRINT Phase I showed similar efficacy.

It is recognised that in the opinion of either the investigator, the patient, or the patient's parents, improvement in clinical outcomes (e.g. QoL, pain intensity, vision scale, motor scales, and disfigurement) were established. Thus when considering ORR in the context of improved clinical outcomes at the patient level, efficacy of selumetinib in patients with NF1 PN can be considered established, at least for the duration of follow-up of the pivotal trial (about 2 years).

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above, the applicant will submit an updated analysis of the study SPRINT Phase II Stratum 1 with a data cut-off of 31 March 2021. The clinical study report will be submitted by 31 March 2022:

In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above, the applicant will submit an updated

analysis of the study SPRINT Phase I with a data cut-off of 27 February 2021. The clinical study report will be submitted by 31 March 2022:

2.6. Clinical safety

The principal source of safety data in paediatric patients with NF1 and inoperable PN derived from the NCI-sponsored open-label SPRINT study. The safety data set included all patients who received at least 1 dose of selumetinib.

Safety data from the following datasets were submitted:

- Pivotal study SPRINT Phase II stratum 1 (N=50, data cut-off 29 June 2018); patients aged ≥3 and ≤18 years (able to swallow whole capsules) received selumetinib 25 mg/m^2 BID as a monotherapy.
- Supportive study SPRINT Phase I (N=24, data cut-off 29 June 2018); in which patients ≥3 and ≤18 years (able to swallow whole capsules), received selumetinib 20 mg/m^2 BID (n=12), 25 mg/m^2 BID (n=6), or 30 mg/m^2 BID (n=6).
- Paediatric safety Pool (N=74), data cut-off 29 June 2018. This population comprised pooled safety data across SPRINT Phase II Stratum I and Phase I studies; it did not include data from SPRINT phase II Stratum I 90-day safety update report. All patients (3 years to 18 years) who received selumetinib at any dose in SPRINT Phase I or Phase II Stratum 1 were included. Safety data from a sub-group of paediatric patients (n=56) who received 25 mg/m^2 on either study as per initial dose assignment was presented separately.
- Longer-term follow up safety data was provided in the SPRINT Phase II Stratum 1 90-day safety update (29 March 2019) report. At the time of the day 90 safety update report (29 March 2019), 44 (88.0%) patients remained within the study.

To support children and their family, some study-mandated evaluations i.e., medical history, physical examinations and laboratory evaluations were conducted by local health care providers (HCPs).

In addition, safety data from 7 studies in adult patients with cancer (n=347) including one phase III study (SUMIT) were submitted. Furthermore, safety data from studies performed as part of the clinical pharmacology program (e.g. pharmacokinetic and drug-drug interactions studies) were also analysed although they had been performed in 380 healthy volunteers.

Patient exposure

Exposure to selumetinib for the SPRINT Paediatric pool and the individual data sub-sets is presented in Table 47.

Table 42: SPRINT Phase II Stratum 1 and the Paediatric pool: Duration of selumetinib exposure (Safety analysis set)

		Phase II Stratum 1 25 mg/m² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m² BID (N=56)	Phase I 20 mg/m² BID (N=12)	Phase I 25 mg/m² BID (N=6)	Phase I 30 mg/m² BID (N=6)	Paediatric pool All doses (N=74)
Total treatment duration (days)[a]	Mean (SD)	725.7 (253.50)	819.2 (362.54)	1519.2 (533.11)	1598.3 (13.84)	1380.0 (700.01)	978.2 (506.14)
	Median (min-max)	801.5 (28-1053)	818.5 (28-1617)	1738.5 (158-2169)	1597.0 (1583-1617)	1409.5 (500-2131)	855.5 (28-2169)
	Total treatment years	99.3	125.6	49.9	26.3	22.7	198.2
Total treatment duration (months)[b]	Mean (SD)	23.8 (8.33)	26.9 (11.91)	49.9 (17.51)	52.5 (0.45)	45.3 (23.0)	32.1 (16.63)
	Median (min-max)	26.3 (1-35)	26.9 (1-53)	57.1 (5-71)	52.5 (52-53)	46.3 (16-70)	28.1 (1-71)
Total treatment duration (months)[b]	<12	6 (12.0)	6 (10.7)	1 (8.3)	0	0	7 (9.5)
	≥12 to ≤24	11 (22.0)	11 (19.6)	0	0	1 (16.7)	12 (16.2)
	>24 to ≤36	33 (66.0)	33 (58.9)	1 (8.3)	0	2 (33.3)	36 (48.6)
	>36 to ≤48	0	0	2 (16.7)	0	0	2 (2.7)
	>48 to ≤60	0	6 (10.7)	5 (41.7)	6 (100.0)	1 (16.7)	12 (16.2)
	>60	0	0	3 (25.0)	0	2 (33.3)	5 (6.8)
Actual treatment duration (days)[c]	Mean (SD)	669.6 (240.98)	755.7 (339.02)	1384.0 (506.03)	1473.3 (54.84)	1189.5 (620.91)	892.7 (461.43)
	Median (min-max)	721.50 (26-1022)	742.5 (26-1539)	1468.5 (139-1995)	1488.5 (1389-1539)	1204.5 (424-1904)	777.8 (26-1995)
	Total treatment years	91.7	115.9	45.5	24.2	19.5	180.9

In the paediatric pool, the median total duration of selumetinib treatment in paediatric patients with NF1 who have PN was 28 months (range: < 1 to 71 months), 23% of patients were exposed to selumetinib treatment for > 48 months.

At the time of the day 90 safety update report (29 March 2019), 44 (88.0%) patients remained within the study; of these, 30 (60.0%) patients, and a further 2 re-treatment patients, were continuing to receive selumetinib. The median total duration of exposure to selumetinib was 1027.50 days (33.8 months), and the median actual exposure was 943.98 days (31.0 months). The maximum actual duration of exposure was 1290 days (42.4 months). At the DCO date of 29 March 2019, 17 (34.0%) patients had >36 months (>3 years) total treatment duration.

Adverse events

As the majority (≥98.0%) of the AEs reported in the SPRINT paediatric population were attributed as related to selumetinib treatment by the Investigators, treatment-related AEs are not presented separately.

Overall incidence of Adverse Events

The paediatric pool, 73/74 (98.6%) patients had at least 1 AE (Table 48).

Table 43: SPRINT Phase II Stratum 1, Phase I and the Paediatric pool: Adverse events in any category

	Number of patients[a]				
	Phase II Stratum 1 25 mg/m² BID (N=50)	Phase I 20 mg/m² BID (N=12)	Phase I 25 mg/m² BID (N=6)	Phase I 30 mg/m² BID (N=6)	Paediatric pool All doses (N=74)
Any AE	49 (98.0)	12 (100)	6 (100)	6 (100)	73 (98.6)
Any AE causally related to selumetinib[b]	49 (98.0)	12 (100)	6 (100)	6 (100)	73 (98.6)
Any AE of CTCAE Grade ≥3	31 (62.0)	8 (66.7)	5 (83.3)	6 (100)	50 (67.6)
Any AE of CTCAE Grade ≥3 causally related to selumetinib[b]	19 (38.0)	5 (41.7)	3 (50.0)	5 (83.3)	32 (43.2)
Any AE with outcome of death	0	0	0	0	0
Any AE with outcome of death causally related to selumetinib[b]	0	0	0	0	0
Any SAE (including events with outcome=death)	12 (24.0)	2 (16.7)	2 (33.3)	1 (16.7)	17 (23.0)
Any SAE (including events with outcome=death), causally related to selumetinib[b]	6 (12.0)	1 (8.3)	1 (16.7)	0	8 (10.8)
Any AE leading to discontinuation of selumetinib	6 (12.0)	1 (8.3)	0	2 (33.3)	9 (12.2)
Any AE leading to dose reduction of selumetinib	12 (24.0)	5 (41.7)	3 (50.0)	4 (66.7)	24 (32.4)
Any AE leading to dose interruption of selumetinib	40 (80.0)	8 (66.7)	5 (83.3)	5 (83.3)	58 (78.4)
Any AE leading to dose modification	40 (80.0)	8 (66.7)	5 (83.3)	5 (83.3)	58 (78.4)

Common adverse events

The most commonly reported SOCs for SPRINT Phase II Stratum 1 and the Paediatric pool were: Investigations, Skin and subcutaneous tissue disorders, Gastrointestinal disorders, Metabolism and nutrition disorders, General disorders and administration site conditions, Infections and infestations, Respiratory, thoracic and mediastinal disorders, Musculoskeletal and connective tissue disorders, and Nervous system disorders.

Table 44: SPRINT Phase II Stratum 1 and the Paediatric pool: Most common AEs (occurring in ≥30% of patients of either the Phase II Stratum 1, the Paediatric pool or the 25mg/m² sub-group) (Safety analysis set)

MedDRA preferred term	Phase II Stratum 1 25 mg/m² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m² BID (N=56)	Phase I 20 mg/m² BID (N=12)	Phase I 25 mg/m² BID (N=6)	Phase I 30 mg/m² BID (N=6)	Paediatric pool All doses (N=74)
Preferred term	**Number (%) of patients[a]**					
Patients with any AE	49 (98.0)	55 (98.2)	12 (100)	6 (100)	6 (100)	73 (98.6)
Vomiting	41 (82.0)	45 (80.4)	10 (83.3)	4 (66.7)	6 (100)	61 (82.4)
Blood creatine phosphokinase increased	38 (76.0)	44 (78.6)	6 (50.0)	6 (100)	6 (100)	56 (75.7)
Diarrhoea	35 (70.0)	40 (71.4)	11 (91.7)	5 (83.3)	6 (100)	57 (77.0)
Nausea	33 (66.0)	37 (66.1)	11 (91.7)	4 (66.7)	6 (100)	54 (73.0)
Dry skin	30 (60.0)	34 (60.7)	6 (50.0)	4 (66.7)	3 (50.0)	43 (58.1)
Fatigue	28 (56.0)	32 (57.1)	7 (58.3)	4 (66.7)	5 (83.3)	44 (59.5)
Pyrexia	28 (56.0)	33 (58.9)	6 (50.0)	5 (83.3)	3 (50.0)	42 (56.8)
Dermatitis acneiform	25 (50.0)	28 (50.0)	6 (50.0)	3 (50.0)	6 (100)	40 (54.1)
Hypoalbuminaemia	25 (50.0)	28 (50.0)	8 (66.7)	3 (50.0)	1 (16.7)	37 (50.0)
Stomatitis	25 (50.0)	27 (48.2)	6 (50.0)	2 (33.3)	5 (83.3)	38 (51.4)
Headache	24 (48.0)	29 (51.8)	6 (50.0)	5 (83.3)	5 (83.3)	40 (54.1)
Oropharyngeal pain	24 (48.0)	25 (44.6)	3 (25.0)	1 (16.7)	2 (33.3)	30 (40.5)
Aspartate aminotransferase increased	23 (46.0)	27 (48.2)	8 (66.7)	4 (66.7)	2 (33.3)	37 (50.0)
Paronychia	23 (46.0)	26 (46.4)	5 (41.7)	3 (50.0)	2 (33.3)	33 (44.6)
Pruritus	23 (46.0)	26 (46.4)	4 (33.3)	3 (50.0)	1 (16.7)	31 (41.9)
Abdominal pain	22 (44.0)	24 (42.9)	7 (58.3)	2 (33.3)	3 (50.0)	34 (45.9)

Anaemia	21 (42.0)	23 (41.1)	8 (66.7)	2 (33.3)	2 (33.3)	33 (44.6)
Abdominal pain upper	20 (40.0)	23 (41.1)	5 (41.7)	3 (50.0)	4 (66.7)	32 (43.2)
Cough	20 (40.0)	26 (46.4)	7 (58.3)	6 (100)	4 (66.7)	37 (50.0)
Pain in extremity	18 (36.0)	19 (33.9)	3 (25.0)	1 (16.7)	4 (66.7)	26 (35.1)
Rash maculo-papular	18 (36.0)	22 (39.3)	4 (33.3)	4 (66.7)	3 (50.0)	29 (39.2)
Alanine aminotransferase increased	17 (34.0)	20 (35.7)	5 (41.7)	3 (50.0)	2 (33.3)	27 (36.5)
Constipation	17 (34.0)	21 (37.5)	2 (16.7)	4 (66.7)	2 (33.3)	25 (33.8)
Nasal congestion	17 (34.0)	21 (37.5)	5 (41.7)	4 (66.7)	6 (100)	32 (43.2)
Neutrophil count decreased	16 (32.0)	18 (32.1)	8 (66.7)	2 (33.3)	4 (66.7)	30 (40.5)
Influenza like illness	15 (30.0)	16 (28.6)	2 (16.7)	1 (16.7)	2 (33.3)	20 (27.0)
Rhinitis allergic	15 (30.0)	15 (26.8)	1 (8.3)	0	0	16 (21.6)
Hypoglycaemia	14 (28.0)	17 (30.4)	3 (25.0)	3 (50.0)	2 (33.3)	22 (29.7)
Otitis media	14 (28.0)	17 (30.4)	2 (16.7)	3 (50.0)	3 (50.0)	22 (29.7)
Hyperglycaemia	11 (22.0)	15 (26.8)	6 (50.0)	4 (66.7)	2 (33.3)	23 (31.1)
Lymphocyte count decreased	10 (20.0)	14 (25.0)	7 (58.3)	4 (66.7)	5 (83.3)	26 (35.1)
White blood cell count decreased	10 (20.0)	12 (21.4)	7 (58.3)	2 (33.3)	4 (66.7)	23 (31.1)

[a] Number (%) of patients with AEs, sorted in decreasing frequency of events in SPRINT Phase II Stratum 1.

Grade ≥3 Adverse Events

For the SPRINT Phase II Stratum 1 and the Paediatric pool, Grade ≥3 AEs were most commonly reported in the SOCs of Gastrointestinal disorders, Infections and infestations, and Investigations.

Table 45: SPRINT Phase II Stratum 1 and the Paediatric pool: Adverse events of CTCAE Grade 3 or higher (occurring in 2 or more patients in the Paediatric pool), by system organ class and preferred term (Safety analysis set)

	Number(%) of patients[a]					
MedDRA SOC and PT	Phase II Stratum 1 25 mg/m2 BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m2 BID (N=56)	Phase I 20 mg/m2 BID (N=12)	Phase I 25 mg/m2 BID (N=6)	Phase I 30 mg/m2 BID (N=6)	Paediatric pool All doses (N=74)
Patients with any AE of CTCAE Grade 3 or higher	31 (62.0)	36 (64.3)	8 (66.7)	5 (83.3)	6 (100)	50 (67.6)
Infections and infestations	9 (18.0)	10 (17.9)	7 (58.3)	1 (16.7)	2 (33.3)	19 (25.7)
Paronychia	3 (6.0)	4 (7.1)	1 (8.3)	1 (16.7)	2 (33.3)	7 (9.5)
Gastroenteritis	0	1 (1.8)	1 (8.3)	1 (16.7)	0	2 (2.7)
Blood and lymphatic system disorders	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Anaemia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Nervous system disorders	3 (6.0)	3 (5.4)	2 (16.7)	0	1 (16.7)	6 (8.1)
Syncope	2 (4.0)	2 (3.6)	1 (8.3)	0	1 (16.7)	4 (5.4)
Headache	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Gastrointestinal disorders	12 (24.0)	14 (25.0)	4 (33.3)	2 (33.3)	2 (33.3)	20 (27.0)
Diarrhoea	8 (16.0)	8 (14.3)	2 (16.7)	0	1 (16.7)	11 (14.9)
Vomiting	3 (6.0)	5 (8.9)	1 (8.3)	2 (33.3)	0	6 (8.1)
Dental caries	2 (4.0)	2 (3.6)	2 (16.7)	0	0	4 (5.4)
Skin and subcutaneous tissue disorders	5 (10.0)	6 (10.7)	1 (8.3)	1 (16.7)	0	7 (9.5)
Dermatitis acneiform	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Eczema	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Rash maculo-papular	1 (2.0)	2 (3.6)	0	1 (16.7)	0	2 (2.7)
General disorders and administration site conditions	4 (8.0)	5 (8.9)	1 (8.3)	1 (16.7)	0	6 (8.1)

Pyrexia	4 (8.0)	5 (8.9)	1 (8.3)	1 (16.7)	0	6 (8.1)
Investigations	10 (20.0)	11 (19.6)	4 (33.3)	1 (16.7)	3 (50.0)	18 (24.3)
Blood creatine phosphokinase increased	3 (6.0)	4 (7.1)	1 (8.3)	1 (16.7)	2 (33.3)	7 (9.5)
Weight increased	3 (6.0)	3 (5.4)	3 (25.0)	0	0	6 (8.1)
Alanine aminotransferase increased	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Lipase increased	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Neutrophil count decreased	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Respiratory, thoracic and mediastinal disorders	4 (8.0)	4 (7.1)	0	0	0	4 (5.4)
Hypoxia	4 (8.0)	4 (7.1)	0	0	0	4 (5.4)

[a] Number (%) of patients with AEs of CTCAE Grade 3 or higher, sorted in decreasing frequency of events in the selumetinib Phase II Stratum 1 treatment group.

Long-term safety evaluation in SPRINT Phase II Stratum 1 over time

In SPRINT Phase II Stratum 1 the expected duration of the long term safety follow up was 7 years following initiation of treatment or 5 years after study drug discontinuation, whichever was longer.

Table 46: SPRINT Phase I: AEs with long term exposure

	Number (%) of patients							
	Year 1 N=24		Year 2 N=23		Year 3 N=20		Year 4 N=17	
MedDRA SOC and PT	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Eye disorders	**1 (4)**	**0**	**1 (4)**	**0**	**1 (5)**	**0**	**0**	**0**
Vision blurred	1 (4)	0	1 (4)	0	1 (5)	0	0	0
Gastrointestinal disorders	**24 (100)**	**1 (4)**	**17 (74)**	**3 (13)**	**13 (65)**	**1 (5)**	**13 (76)**	**2 (12)**
Diarrhoea	16 (66)	0	10 (43)	1 (4)	5 (25)	1 (5)	9 (53)	2 (12)
Dry mouth	2 (8)	0	0	0	0	0	0	0
Nausea	18 (75)	0	11 (48)	0	4 (20)	0	3 (18)	0
Stomatitis	9 (38)	0	6 (26)	1 (4)	4 (20)	0	5 (29)	0
Vomiting	19 (79)	1 (4)	11 (48)	1 (4)	10 (50)	1 (5)	4 (24)	0
General disorders and administration site conditions	**20 (83)**	**1 (4)**	**10 (43)**	**0**	**7 (35)**	**0**	**5 (29)**	**1 (6)**
Face oedema	2 (8)	0	0	0	1 (5)	0	0	0
Fatigue	14 (58)	0	5 (22)	0	4 (20)	0	1 (6)	0
Oedema peripheral	0	0	0	0	0	0	1 (6)	0
Pyrexia	10 (42)	1 (4)	5 (22)	0	2 (10)	0	3 (18)	1 (6)
Investigations	**23 (96)**	**3 (13)**	**21 (91)**	**1 (4)**	**19 (95)**	**0**	**15 (88)**	**1 (6)**
Alanine aminotransferase increased	7 (29)	0	2 (9)	0	2 (10)	0	1 (6)	0
Anaemia	7 (29)	0	4 (17)	0	4 (20)	0	7 (41)	0
Aspartate aminotransferase increased	9 (38)	0	6 (26)	0	5 (25)	0	5 (29)	0
Blood creatine phosphokinase increased	18 (75)	2 (8)	14 (61)	1 (4)	10 (50)	0	9 (53)	1 (6)
Blood creatinine increased	6 (25)	0	5 (22)	0	2 (10)	0	0	0
Ejection fraction decreased	2 (8)	1 (4)	0	0	2 (10)	0	2 (12)	0
Hypertension	3 (13)	0	0	0	1 (5)	0	0	0
Hypoalbuminaemia	10 (42)	0	5 (22)	0	6 (30)	0	4 (24)	0
Respiratory, thoracic and mediastinal disorders	**1 (4)**	**0**	**0**	**0**	**1 (5)**	**0**	**1 (6)**	**0**
Dyspnoea	1 (4)	0	0	0	1 (5)	0	1 (6)	0
Skin and subcutaneous tissue disorders	**21 (88)**	**1 (4)**	**12 (52)**	**2 (9)**	**10 (50)**	**1 (5)**	**8 (47)**	**1 (6)**
Alopecia[a]	6 (25)	0	3 (13)	0	1 (5)	0	0	0
Dermatitis acneiform	10 (42)	0	5 (22)	0	1 (5)	0	3 (18)	0
Dry skin	9 (38)	0	4 (17)	0	1 (5)	0	1 (6)	0
Hair colour changes	7 (29)	0	1 (4)	0	1 (5)	0	0	0
Paronychia	4 (17)	0	4 (17)	2 (9)	5 (25)	1 (5)	4 (24)	1 (6)
Rash erythematous	1 (4)	0	0	0	0	0	0	0
Rash maculo-papular	6 (25)	1 (4)	3 (13)	0	3 (15)	0	2 (12)	0

[a] PT alopecia (reported term: Hair thinning).
Includes data from SPRINT Phase I only.

Safety data during long term follow up

In the SPRINT Phase II Stratum 1 90 days update safety report (90DSU DCO; 29 March 2019), the most frequently reported AEs were the same as those reported at the final CSR (29 June 2018).

The cumulative total number of patients for whom AEs Grade ≥3 were reported at the DCO 29 March 2019, remained the same as reported in the final CSR (31 [62.0%] patients).

At the DCO 29 March 2019, a Grade ≥3 dermatitis acneiform was reported for 1 additional patient compared with the final CSR (6.0% vs 4.0% of patients, respectively). The most commonly reported AEs of Grade ≥3, in the 90 days update safety report remained consistent with those in the final CSR.

At the DCO 29 March 2019, no new-treatment emergent SAEs were reported. However, 1 additional patient had Grade 3 SAE of Malignant peripheral nerve sheath tumours (MPNST) that was considered not treatment emergent and hence not included in the 90 days update safety report.

Adverse drug reactions (ADRs)

The table below presents the adverse reactions identified in the paediatric population with NF1 who have inoperable PN and in adult patients. The frequency is determined from the paediatric pool (N = 74); comprises 50 patients from SPRINT phase II stratum 1 and 24 patients from supportive SPRINT phase I dataset. ADRs are organised by MedDRA system organ class (SOC).

Table 47: **Adverse drug reactions reported in the paediatric pool (SPRINT phase II stratum 1 [N = 50] and supportive SPRINT phase I [N = 24]) and in other identified clinical trials in adult patients (N = 347)††**

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE grades) NF1 paediatric pool‡ (N = 74)	Frequency of CTCAE grade 3 and Above† NF1 paediatric pool‡ (N = 74)
Eye disorders	Vision blurred^	Common (9%)	-
Respiratory, thoracic & mediastinal disorders	Dyspnoea*	Common (5%)	-
Gastrointestinal disorders	Vomiting^	Very common (82%)	Common (8%)
	Diarrhoea^	Very common (77%)	Very common (15%)
	Nausea^	Very common (73%)	Common (1%)
	Stomatitis^	Very common (38%)	Common (1%)
	Dry mouth	Common (5%)	-
Skin and subcutaneous tissue disorders	Rash ^ *	Very common (80%)	Common (5%)
	Dry skin	Very common (58%)	-
	Rash acneiform^ *	Very common (54%)	Common (3%)
	Paronychia^	Very common (45%)	Common (9%)
	Hair changes^ *	Very common (39%)	-
General disorders	Asthenic events*	Very common (59%)	-
	Pyrexia	Very common (57%)	Common (8%)
	Peripheral oedema*	Very common (12%)	-
	Facial oedema*	Common (7%)	-
Investigations	Blood CPK increased^	Very common (76%)	Common (9%)
	Hypoalbuminaemia	Very common (50%)	-
	AST increased	Very common (50%)	Common (1%)
	Haemoglobin decreased*	Very common (45%)	Common (3%)
	ALT increased	Very common (36%)	Common (3%)
	Blood creatinine increased	Very common (28%)	Common (1%)
	Ejection fraction decreased^	Very common (23%)	Common (1%)
	Increased blood pressure*	Very common (16%)	-
Eye disorders	Retinal pigment epithelial detachment (RPED)/ Central serous retinopathy (CSR)* ††	Uncommon (0.6%)	-
	Retinal vein occlusion (RVO)* ††	Uncommon (0.3%)	-

Per National Cancer Institute CTCAE version 4.03
CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
^ See Description of selected adverse reactions
† All reactions 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.
†† 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 population with NF1 who have inoperable PN.
‡ Paediatric pool (N=74) percentage rounded to the nearest decimal.
*ADRs based on grouping of individual preferred terms (PT):
Asthenic events: asthenia, fatigue,
CSR/RPED: Detachment of macular retinal pigment epithelium, chorioretinopathy
Dyspnoea: dyspnoea exertional, dyspnoea, dyspnoea at rest
Facial oedema: face odema, periorbital oedema
Haemoglobin decreased: anaemia, haemoglobin decreased
Hair changes: alopecia, hair colour change
Increased blood pressure: blood pressure increased, hypertension
Peripheral oedema: oedema peripheral, oedema
Rash (acneiform): dermatitis acneiform
Rash: dermatitis acneiform, rash maculo-papular, rash papular, rash, rash erythematous, rash macular
RVO: retinal vascular disorder, retinal vein occlusion, retinal vein thrombosis

Adverse Events of Special Interest

Retinal events

Table 48: Adverse events of Retinal events (medical concept) reported in any category in the SPRINT Paediatric pool (Safety analysis set)

AE category	Number (%) of patients [a]	
	SPRINT Phase II Stratum 1 25 mg/m^2 BID (N=50)	Paediatric pool All Doses (N=74)
AESI Term: RPED/central serous retinopathy events, retinal vein occlusion events, other retinal disorders [b]		
Any AE	8 (16.0)	12 (16.2)
Any AE of CTCAE Grade 3 or higher	0	0
AESI Sub-group term: Other retinal disorders/PT		
Chorioretinal scar	1 (2.0)	1 (1.4)
AESI Sub-group term: Visual disorders/PT		
Photophobia	2 (4.0)	3 (4.1)
Vision blurred	4 (8.0)	7 (9.5)
Vitreous disorder	1 (2.0)	1 (1.4)
AESI Sub-group term: Retinal vein occlusion/PT		
Retinal vein occlusion	0	0
AESI Sub-group term: Retinal pigment epithelial detachment/PT		
Retinal pigment epithelial detachment,	0	0
AESI Sub-group term: Central serous retinopathy/PT		
Central serous retinopathy	0	0

[a] Patients with multiple events reported in the same grouped / PT are counted only once in that grouped / PT. Patients with events in more than 1 grouped / PT are counted once in each of those grouped / PTs.

[b] Grouped term consisting of the SMQ of retinal disorders, RPED events, central serous retinopathy events, retinal vein occlusion events, other retinal disorders.

AEs of visual disorder were all Grade 1 or Grade 2; no AEs Grade ≥3 were reported. Two of the 11 patients with AEs in the sub-group term of visual disorder events experienced an event which led to selumetinib dose interruption; none of the visual disorder events led to discontinuation. Nine (9) patients recovered and for 2 patients, outcome was not recovered or not reported.

Other visual disorder events that were reported in the trial population include: chorioretinal scar, photophobia and vitreous disorder. Each of these were reported once.

One patient had an AE of Grade 1 chorioretinal scar (1.4%). The AE did not lead to selumetinib dose modification or discontinuation and had an outcome of not recovered or not reported.

A single event of RPED was reported in a paediatric patient receiving selumetinib monotherapy (25 mg/m2 twice daily) for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study

For selumetinib the reported retinal effect was in general, mild or moderate in severity, did not lead to treatment discontinuation, were manageable by standard supportive therapies, and generally resolved during continued treatment with selumetinib.

Cardiac events

Table 49: Adverse events of Cardiac events (medical concept) reported in any category in the SPRINT Paediatric pool (Safety analysis set)

AE category	Number (%) of patients [a]	
	SPRINT Phase II Stratum 1 25 mg/m^2 BID (N=50)	Paediatric pool All Doses (N=74)
AESI Term: Ejection fraction decreased, other cardiac events [b]		
Any AE	18 (36.0)	26 (35.1)
Any AE of CTCAE Grade 3 or higher	0	1 (1.4)
AESI Sub-group term: Ejection fraction decreased/PT		
Ejection fraction decreased	11 (22.0)	17 (23.0)
AESI Sub-group term: Oedema/PT		
Oedema peripheral	6 (12.0)	9 (12.2)
Peripheral swelling	1 (2.0)	1 (1.4)
AESI Sub-group term: Other cardiac events/PT		
Right ventricular ejection fraction decreased	1 (2.0)	1 (1.4)

[a] Patients with multiple events reported in the same grouped / PT are counted only once in that grouped / PT. Patients with events in more than 1 grouped / PT are counted once in each of those grouped / PTs.

[b] Grouped term consisting of the SMQ of cardiac failure and PTs ejection fraction decreased and other cardiac events.

Includes AEs with an onset on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

Most AEs of ejection fraction decreased were Grade 2. In the paediatric pool, ejection fraction decreased events led to selumetinib dose interruption and dose reduction in 1 (1.4%) patient each; none of the ejection fraction decreased events led to discontinuation. Of the 17 patients with an AE in the sub-group term of ejection fraction decreased events, 12 recovered and for 5 patients their outcome was not recovered or not reported.

In SPRINT, phase II stratum 1, LVEF reduction was reported in 11 (22%) patients; all cases were grade 2, asymptomatic and did not lead to dose interruptions, reductions or discontinuation. Of the 11 patients, 6 patients recovered and for 5 patients the outcome was not reported. The median time to first occurrence of LVEF reduction was 226 days (median duration 78 days). The majority of LVEF reduction adverse reactions were reported as reductions from baseline (⩾ 10% reduction) but were considered to remain in the normal range. Patients with LVEF lower than the institutional LLN at baseline were not included in the pivotal study. In addition, 2 serious cases of LVEF reduction associated with selumetinib have been reported in paediatric patients who participated in an expanded access program.

In the 90 days update safety report (DCO 29 March 2019), 3 patients had recurrent AEs of ejection fraction decreased.

Oedema events

In the paediatric pool, AEs in the sub-group term of oedema events were reported for 13.5% (10/74) of the patients. AEs were all Grade 1. One had an oedema event which led to selumetinib dose interruption. None of the oedema events led to discontinuation. Of the 10 patients with an AE in the sub-group term of oedema events, 6 patients recovered and for 4 patients their outcome was not recovered or not reported. None of the AEs of oedema were associated with any other AE suggesting a cardiac origin.

Other cardiac events

One other cardiac event was reported in one paediatric patient; right ventricular dysfunction. This AE was grade 1. The event did not lead to selumetinib dose modification or discontinuation and was reported as resolved.

Skin and mucous membrane events

Acneiform rash

Table 50: Adverse events of acneiform rash (grouped term) reported in the SPRINT Paediatric pool (Safety analysis set)

AE category	Number (%) of patients [a]	
	SPRINT Phase II Stratum 1 25 mg/m² BID (N=50)	Paediatric pool All Doses (N=74)
AESI Term: Acneiform rash [b]		
Any AE	25 (50.0)	40 (54.1)
Any AE of CTCAE Grade 3 or higher	2 (4.0)	2 (2.7)
AESI/PT		
Dermatitis acneiform	25 (50.0)	40 (54.1)

[a] Patients with multiple events in the same grouped / PT are counted only once in that grouped / PT. Patients with events in more than 1 grouped / PT are counted once in each of those grouped / PTs.

[b] Grouped term consisting of the HLTs of acnes and pustular conditions.

Two patients experienced an AE of acneiform rash that led to selumetinib dose interruption, no patients experienced AEs leading to selumetinib dose reduction or to permanent discontinuation of selumetinib. Of the 40 patients with an AE in the grouped term of acneiform rash, 15 patients recovered and for 25 patients their outcome was not recovered or not reported.

In SPRINT, phase II stratum 1, acneiform rash was observed in 25 (50%) patients (median time to onset 13 days; median duration of 60 days for the maximum CTCAE grade event). The majority of these cases were grade 1 or 2, observed in post-pubertal patients (> 12 years) and did not require any dose interruptions or reductions. Grade 3 adverse reactions were reported for 4%.

Non-acneiform rash

Table 51: Adverse events of non-acneiform rash (grouped term) reported in any category in the SPRINT Paediatric pool (Safety analysis set)

AE category	Number (%) of patients [a]	
	SPRINT Phase II Stratum 1 25 mg/m² BID (N=50)	Paediatric pool All Doses (N=74)
AESI Term: Non-acneiform rash [b]		
Any AE	35 (70.0)	48 (64.9)
Any AE of CTCAE Grade 3 or higher	1 (2.0)	2 (2.7)
AESI/PT		
Pruritus	23 (46.0)	31 (41.9)
Rash	3 (6.0)	3 (4.1)
Rash erythematous	1 (2.0)	2 (2.7)
Rash maculo-papular	18 (36.0)	29 (39.2)
Rash pruritic	1 (2.0)	1 (1.4)

[a] Patients with multiple events in the same grouped / PT are counted only once in that grouped / PT. Patients with events in more than 1 grouped / PT are counted once in each of those grouped / PTs.

[b] Grouped term consisting of the HLT of rashes, eruptions and exanthems NEC and the PT of pruritus NEC.

In the paediatric pool 64.9% (48/74) of the patients experienced an AE of non-acneiform rash, of which 2 were Grade ≥3 of severity. Five patients experienced an AE of non-acneiform rash that led to selumetinib dose interruption, in 2 patients the AE led to selumetinib dose reduction. In none of the patients the AE of non-acneiform rash led to permanent discontinuation of selumetinib. Of the 48 patients with an AE in the grouped term of non-acneiform rash, 29 patients recovered and for 19 patients their outcome was not recovered or not reported. In SPRINT, phase II stratum 1, other (non-acneiform) rashes were observed in 35 (70%) patients in the pivotal study and were predominantly grade 1 or 2.

Nail disorder events

In the paediatric pool, 64.9% of the patients (34/74) experienced an AE of nail disorders, of which 33 patients (44.6%) had paronychia. Seven patients had an AE of Grade ⩾3. Also, in 7 patients the AE led to selumetinib dose interruption, 4 patients experienced AEs leading to selumetinib dose reduction, and 1 patient experienced an AE which led to permanent discontinuation of selumetinib. Of the 34 patients (45.9%) with an AE in the grouped term of nail disorder events, 24 patients recovered and for 10 patients their outcome was not recovered or not reported. The majority of the patients responded to dose modification and additional symptomatic/ supportive treatment.

In SPRINT, phase II stratum 1, paronychia was reported in 23 (46%) patients, the median time to first onset of maximum grade paronychia adverse reaction was 306 days and the median duration of adverse reactions was 96 days. The majority of these adverse reactions were grade 1 or 2 and were treated with supportive or symptomatic therapy and/or dose modification. Grade ⩾ 3 events occurred in three (6%) patients. Seven patients (3 with a maximum grade 3 adverse reaction and 4 with a maximum grade 2 adverse reaction) had a selumetinib dose interruption for adverse reactions of paronychia, of whom 3 had dose interruption followed by dose reduction (2 patients required a second dose reduction). In one patient (2%) the event led to discontinuation.

Oral mucositis

In the paediatric pool 52.7% of the patients (39/74) had an AE of oral mucositis. Most of the patients had stomatitis. Five patients experienced an AE which led to selumetinib dose interruption, 2 patients experienced AEs leading to selumetinib dose reduction; 1 patient had an AE which led to permanent discontinuation of selumetinib. Of the 39 patients with an oral mucositis, 31 recovered and for 8 patients their outcome was not recovered or not reported.

One patient treated with 30 mg/m^2 selumetinib, discontinued treatment after multiple events of stomatitis, the highest being Grade 3. This patient also had multiple dose interruptions due to stomatitis, in addition to an interruption followed by dose reduction.

Muscular events

Table 52: Adverse events of Muscular events (medical concept) reported in any category in the SPRINT Paediatric pool (Safety analysis set)

AE category	Number (%) of patients [a]	
	SPRINT Phase II Stratum 1 25 mg/m^2 BID (N=50)	Paediatric pool All Doses (N=74)
AESI Term: Muscle events, CPK increased [b]		
Any AE	43 (86.0)	65 (87.8)
Any AE of CTCAE Grade 3 or higher	4 (8.0)	8 (10.8)
AESI Sub-group term: CPK increased/PT		
Blood creatine phosphokinase increased	38 (76.0)	56 (75.7)
Blood creatinine increased	14 (28.0)	21 (28.4)
AESI Sub-group term: Muscle events/PT		
Muscular weakness	1 (2.0)	3 (4.1)
Musculoskeletal pain	3 (6.0)	4 (5.4)
Myalgia	0	6 (8.1)
AESI Sub-group term: Other events/PT		
Acute kidney injury	1 (2.0)	1 (1.4)
Chromaturia	0	1 (1.4)
Hypocalcaemia	12 (24.0)	19 (25.7)

[a] Patients with multiple events reported in the same grouped / PT are counted only once in that grouped / PT. Patients with events in more than 1 grouped / PT are counted once in each of those grouped / PTs.

[b] Grouped term consisting of the SMQ of rhabdomyolysis/myopathy and the PTs of muscle events and CPK increased.

- Elevation of creatine phosphokinase (CPK)

AEs were predominantly Grade 1 or Grade 2 (55 [74.3%] patients). Five patients (6.8%) had AEs of Grade 3 and 3 (4.1%) patients had AEs of Grade 4. In 5 patients an AE of CPK elevation led to selumetinib dose reduction and 1 patient experienced an AE which led to discontinuation. The majority of the CPK increase events did not require either dose modification or symptomatic/ supportive treatment and recovered whilst on selumetinib treatment. For the 63 patients with an AE of CPK increased events, 39 patients recovered and for 24 patients their outcome was not recovered or not reported.

Adverse reactions of blood CPK elevation occurred in 76% of patients in SPRINT phase II stratum 1. The median time to first onset of the maximum grade CPK increase was 106 days and the median duration of adverse reactions was 126 days. The majority of adverse reactions were grade 1 or 2 and resolved with no change in selumetinib dose. Grade $\geqslant$ 3 adverse reactions occurred in three (6%) patients. A grade 4 adverse reaction led to treatment interruption followed by dose reduction.

- Muscle events

AEs were predominantly Grade 1 or Grade 2 (10 [13.5%] patients), AEs of Grade 3 were reported by 1 (1.4%) patient; no AEs of Grade 4 or 5 were reported.

In 6 patients, AEs of CPK increased and myalgia occurred concurrently. In all of these patients, after the concurrent occurrence of myalgia or muscle weakness with blood CPK increased, there were other events of blood CPK increased reported on treatment with selumetinib. However, myalgia or muscle weakness did not reoccur at these time moments.

One of the 11 patients with AEs in the sub-group term of muscle events experienced an event which led to selumetinib dose interruption and 1 patient had an event which led to selumetinib discontinuation. All AEs in the sub-group term of muscle events in the Paediatric pool, were reported as recovered.

Physeal dysplasia

In non-clinical rat studies, physeal dysplasia has been reported after treatment with MEK inhibitors, including selumetinib. In order to ascertain the risk of physeal dysplasia in the paediatric population, a

surrogate marker of height was used to ascertain the effect on growth plate. The hypothesis was as follows: if selumetinib did affect the growth plate in children, it would also affect the height and linear growth. No deviating growth pattern was seen for children treated with selumetinib in comparison to natural history patients.

Gastrointestinal (GI) toxicity

In the paediatric pool an incidence of gastrointestinal AEs (about 97% of the patient had at least one GI AE), including vomiting (82%) diarrhoea (70%) and nausea (66%), was reported. Grade 3 or higher events occurred in 27% of the patients in the Paediatric pool, 14.4% of the patients had a Grade ≥ 3 event of diarrhoea and 8.1% of vomiting. Gastrointestinal SAEs occurred in 5.4% of the patients. Two patients (2.7%) had a SAE of diarrhoea.

In SPRINT, phase II stratum 1, vomiting (41 patients, 82%, median duration 3 days), diarrhoea (35 patients, 70%, median duration 5 days), nausea (33 patients, 66%, median duration 16 days), and stomatitis (25 patients, 50%, median duration 12 days) were the most commonly reported gastrointestinal (GI) reactions. The majority of these cases were grade 1 or 2 and did not require any dose interruptions or dose reductions.

Grade 3 adverse reactions were reported for diarrhoea (8 patients, 16%), nausea (1 patient, 2%), and vomiting (3 patients, 6%). For one patient diarrhoea led to dose reduction and subsequent discontinuation. No dose reduction or discontinuation was required for adverse reactions of nausea, vomiting or stomatitis.

Hair changes

In SPRINT, phase II stratum 1, 32% of patients experienced hair changes (reported as hair lightening [PT: hair colour changes] in 11 patients (22%) and hair thinning [PT: alopecia]) in 12 patients (24%)); in 7 patients (14%) both alopecia and hair colour changes were reported during treatment. All cases were grade 1 and did not require dose interruption or dose reduction.

Weight increased

Certain events of weight increased were classified as AEs in SPRINT Phase II study based on the fact that these events were managed through selumetinib dose modification by the investigator.

Three patients out of 50 experienced weight increased during SPRINT phase II study and another one reported after the 90DSU DCO. All of the events were Grade 3 and were considered to be non-serious. All of the events resulted in selumetinib dose modification; two patients had an interruption and 1 patient had an interruption followed by a dose reduction. Two patients recovered and the outcome was unknown for the remaining patients.

Overdose

During clinical trials SPRINT phase II and I, 4 and 3 patients experienced selumetinib overdose. Most of these cases did not lead to adverse events. In SPRINT phase II, one patient experienced CTCAE Grade 2 phlebitis which was attributed by the investigator to selumetinib and resulted in dose interruption. In SPRINT Phase I CTCAE Grade 2 paronychia was considered by the investigator to be unlikely related to selumetinib and possibly related to family history, and it did not result in dose modification. A case of overdose was reported in a 14-year-old female patient who was receiving selumetinib for NF1-PN in the Early Access Protocol and she experienced CTCAE Grade 1 dizziness, abdominal pain, and vomiting as well as CTCAE Grade 2 dermatitis acneiform. The reporting physician assessed the AE of dizziness to be serious. The investigator considered the AEs of dizziness, abdominal pain, and vomiting to be causally related to the overdose, given there was a rapid and complete recovery after dose reduction to 35 mg BID. However, the dermatitis acneiform persisted after dose reduction.

Serious adverse event/deaths/other significant events

Eight (16.0%) patients in SPRINT Phase II Stratum 1 and 11 (14.9%) patients in the paediatric pool, had AEs that led to hospitalisation.

Table 53: Sprint Phase II stratum 1 and the Paediatric pool: SAE by SOC and PT, (occurring in ≥ 2 patients in any group) in SPRINT (Safety analysis set)

MedDRA SOC and PT	Number (%) of patients[a]					
	Phase II Stratum 1 25 mg/m² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m² BID (N=56)	Phase I 20 mg/m² BID (N=12)	Phase I 25 mg/m² BID (N=6)	Phase I 30 mg/m² BID (N=6)	Paediatric pool All doses (N=74)
Patients with any SAE	12 (24.0)	14 (25.0)	2 (16.7)	2 (33.3)	1 (16.7)	17 (23.0)
Blood and lymphatic disorders	**2 (4.0)**	**2 (3.6)**	**0**	**0**	**0**	**2 (2.7)**
Anaemia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Respiratory, thoracic and mediastinal disorders	**2 (4.0)**	**2 (3.6)**	**0**	**0**	**0**	**2 (2.7)**
Hypoxia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Gastrointestinal disorders	**3 (6.0)**	**4 (7.1)**	**0**	**1 (16.7)**	**0**	**4 (5.4)**
Diarrhoea	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
General disorders and administration site conditions	**1 (2.0)**	**1 (1.8)**	**1 (8.3)**	**0**	**0**	**2 (2.7)**
Pyrexia	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Investigations	**2 (4.0)**	**3 (5.4)**	**0**	**1 (16.7)**	**0**	**3 (4.1)**
Blood creatine phosphokinase increased	1 (2.0)	2 (3.6)	0	1 (16.7)	0	2 (2.7)

[a] Number (%) of patients with an SAE, sorted by SOC and then in decreasing frequency of events in the Phase II Stratum 1 treatment group

Patients with multiple SAEs are counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

AE Adverse event; BID Twice daily, CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical dictionary for regulatory activities (version 21.0); PT Preferred term; SOC System organ class.

Serious Adverse events of interest

Malignant peripheral nerve sheath tumours (MPNST)

NF1 represents a major risk factor for development of malignancy, in particular MPNST. In SPRINT Phase II Stratum 1, two AEs of MPNST were reported; one AE was reported during treatment with selumetinib and one AE occurred 6 months after selumetinib was discontinued. In the 90 days updated Safety report one addition MPNST event was reported. This patient had already stopped treatment with selumetinib.

Laboratory findings

Samples for measurement of clinical laboratory parameters were collected at screening, at intervals throughout the treatment period (depending on the parameter pre-every 1, 2 or 4 cycles) and during the follow-up period. Any abnormal laboratory values were to be followed until return to baseline or stabilisation of event.

Changes from baseline over time in haematology variables

In SPRINT Phase II Stratum 1 and the paediatric pool most commonly reported grade changes were reported for haemoglobin (28.6% and 39.7%, respectively) and neutrophils (low) (33.3% and 41.7%, respectively).

Grade changes for haemoglobin were mostly a 1-grade shift increase from baseline. In the SPRINT Phase II stratum 1 population and in the paediatric pool, 4.1% (2/49) and 2.7% (2/73) of the patients

experienced a 2-grade shift. Three-grade shift was reported for 4.1% (2/49) and 2.7% (2/73) of the patients of the SPRINT Phase II Stratum 1 study and the paediatric pool respectively.

Grade changes for neutrophils (low) were reported for 10.4% and 13.9% of the patients in the SPRINT Phase II stratum 1 population and in the paediatric pool. Two-grade shift from baseline were reported for respectively 18.8% (9/48) and 23.6% (17/72) of the patients, 4.2% (2/48) and 4.2% (3/72) of the patients of the SPRINT Phase II Stratum 1 study and the paediatric pool had 3-grade shift from baseline.

Table 54: SPRINT Phase II Stratum 1 and the Paediatric pool: Number (%) of patients with maximum overall CTCAE grades during selumetinib treatment for key haematological parameters (Safety analysis set)

Laboratory parameter	Evaluable patients*	Maximum overall CTCAE grade during treatment (%)[b]				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SPRINT Phase II Stratum 1: 25 mg/m² BID (N=50)						
Haemoglobin (Low)	49 (98.0)	29 (59.2)	15 (30.6)	3 (6.1)	2 (4.1)	0
Neutrophils (Low)	49 (98.0)	33 (67.3)	5 (10.2)	9 (18.4)	2 (4.1)	0
Lymphocytes (Low)	49 (98.0)	38 (77.6)	8 (16.3)	2 (4.1)	1 (2.0)	0
Platelets (Low)	49 (98.0)	44 (89.8)	5 (10.2)	0	0	0
Paediatric pool: All Doses (N=74)						
Haemoglobin (Low)	73 (98.6)	43 (58.9)	25 (34.2)	3 (4.1)	2 (2.7)	0
Neutrophils (Low)	73 (98.6)	43 (58.9)	8 (11.0)	19 (26.0)	3 (4.1)	0
Lymphocytes (Low)	73 (98.6)	48 (65.8)	21 (28.8)	3 (4.1)	1 (1.4)	0
Platelets (Low)	73 (98.6)	66 (90.4)	7 (9.6)	0	0	0

* Patients with at least 1 on treatment value, were used for calculation of percentages.

[b] Derived from laboratory assessments between first dose of selumetinib and up to and including 30 days following the date of last dose of selumetinib, and is the maximum CTCAE grade (Low/High).

Patients with no Low/High graded assessments during treatment were excluded.

CTCAE version 4.0.3.

BID Twice daily; CTCAE = Common Terminology Criteria for Adverse Events; ISS Integrated Summary of Safety.

Clinical chemistry

In the SPRINT Phase II Stratum study and paediatric pool, grade changes were most commonly seen for creatinine (high); respectively 63.3% and 56.2% of patients experienced a 1-grade shift increase from baseline, 32.7% and 41.1% patients experienced a 2-grade shift increase from baseline, and 2.0% and 1.4% patient experienced a 4-grade shift increase from baseline.

The next most commonly seen grade change was for creatinine kinase (high); respectively, 59.2% and 50.7% of patients experienced a 1-grade shift increase from baseline, 6.1% and 12.3% of patients experienced a 2-grade shift increase from baseline, 4.1% and 6.8% patients experienced a 3-grade shift increase from baseline, and 2.0% and 2.7% patients experienced a 4-grade shift increase from baseline.

Table 55: SPRINT Phase II Stratum 1 and the Paediatric pool: Number (%) of patients with maximum overall CTCAE grades during selumetinib treatment for key clinical chemistry parameters (Safety analysis set)

Laboratory parameter	Evaluable patients [a]	Maximum overall CTCAE grade during treatment (%) [b]				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
SPRINT Phase II Stratum 1: 25 mg/m^2 BID (N=50)						
Albumin (Low)	49 (98.0)	25 (51.0)	19 (38.8)	5 (10.2)	0	0
AST (High)	49 (98.0)	27 (55.1)	18 (36.7)	3 (6.1)	1 (2.0)	0
ALT (High)	49 (98.0)	32 (65.3)	15 (30.6)	0	2 (4.1)	0
Creatine kinase (High)	49 (98.0)	14 (28.6)	29 (59.2)	3 (6.1)	2 (4.1)	1 (2.0)
Creatinine (High)	49 (98.0)	1 (2.0)	31 (63.3)	16 (32.7)	0	1 (2.0)
Bilirubin (High)	49 (98.0)	48 (98.0)	1 (2.0)	0	0	0
Paediatric pool: All Doses (N=74)						
Albumin (Low)	73 (98.6)	37 (50.7)	28 (38.4)	8 (11.0)	0	0
AST (High)	73 (98.6)	38 (52.1)	31 (42.5)	3 (4.1)	1 (1.4)	0
ALT (High)	73 (98.6)	47 (64.4)	24 (32.9)	0	2 (2.7)	0
Creatine kinase (High)	73 (98.6)	20 (27.4)	37 (50.7)	9 (12.3)	5 (6.8)	2 (2.7)
Creatinine (High)	73 (98.6)	1 (1.4)	41 (56.2)	30 (41.1)	0	1 (1.4)
Bilirubin (High)	73 (98.6)	68 (93.2)	4 (5.5)	1 (1.4)	0	0

[a] Patients with at least one on treatment value, used for calculation of percentages.

[b] Derived from Lab assessments between first dose of selumetinib and up to and including 30 days following the date of last dose of selumetinib, and is the maximum CTCAE grade (low/high).

Hepatic biochemistry

In SPRINT Phase II Stratum 1 and the paediatric pool, the majority of patients had a maximum on-treatment AST and ALT increase below 3 × ULN.

None of the patients for whom elevations of either ALT or AST levels were reported, had preceding or coincident elevations in total bilirubin.

Renal biochemistry

Sixteen (32.7%) patients in SPRINT Phase II Stratum 1 had a high BUN on treatment, 1 of which had a high BUN value at baseline. Twenty-four patients had high BUN in the Paediatric pool, 2 of which had a high value at baseline.

Creatinine increased

In SPRINT Phase II Stratum 1, 14 (28.0%) patients had an AE of blood creatinine increased; the majority of these were Grade 1, with 4 (8.0%) patients with a Grade 2 AE and 1 patient (2.0%) with a Grade 4 AE.

In the paediatric pool, 21 (28.4%) patients had an AE of blood creatinine increased; the majority of these were Grade 1, with 7 (9.5%) patients with a Grade 2 AE and 1 (1.4%) patient with a Grade 4 AE. One patient experienced an AE of creatinine increased which was considered related to an SAE of acute kidney injury.

Increased creatinine AEs occurred not simultaneously with changes in other renal function biochemistry tests (urea, BUN).

Urinalysis

There were no clinically significant changes noted.

Other Laboratory values

Overall comparison of data from SPRINT Phase II Stratum 1 and the paediatric pool showed that there were no clinically significant changes in calcium, glucose, magnesium, potassium or sodium observed during treatment.

Safety in special populations

Effect of age

In the paediatric pool, AEs were reported for 44 (97.8%) patients aged 2 to 11 years of age; 24 (100%) of patients aged 12 to 16 years of age and 5 (100%) patients aged >16 years of age. The number of patients in the paediatric pool aged >16 years (n=5) was too small to provide a meaningful comparison.

The overall incidence of AEs in each category were broadly similar for patients aged 2 to 11 years compared with patients aged 12 to 16 years; however, the incidence of AEs leading to hospitalisation were higher for the younger population, i.e., AEs leading to hospitalisation were reported for 22.2% for patients aged 2 to 11 years vs 4.2% for patients aged 12 to 16 years.

AEs of Grade ≥3 were reported for 71.1% of patients in the ≥2 to 11 years age group, compared with 58.3% patients in the 12 to 16 years age group.

SAEs were reported for 26.7% of patients in the ≥2 to 11 years age group, 20.8% in the 12 to 16 years age group.

AEs by SOC and PT were generally reported at similar incidences for all age groups in the paediatric pool.

Patients aged ≥ 2 to 11 years (N = 45) had a higher incidence of the following adverse drug reactions (ADRs) compared to patients aged 12 to 18 years (N = 29): hypoalbuminaemia, dry skin, pyrexia, hair colour changes.

Dermatitis acneiform occurred at a higher frequency in the 12 to 16 years age group. Rash maculo-papular was seen more commonly in patients in the ≥2 to 11 than in the older age group.

Table 56: SPRINT Paediatric pool: Adverse events by age (Safety analysis set)

MedDRA PT	Number (%) of patients		
	≥2 to 11 years (N=45)	12 to 16 years (N=24)	>16 years (N=5)
AEs of relevance with an increased incidence of >10 pp and a ≥2-fold difference in patients aged ≥2 to 11 years compared with patients aged 12 to 16 years, n (%)			
Hypoalbuminaemia	30 (66.7)	6 (25.0)	1 (20.0)
Dry skin	33 (73.3)	8 (33.3)	2 (40.0)
Pyrexia	33 (73.3)	8 (33.3)	1 (20.0)
Hair colour changes	16 (35.6)	3 (12.5)	1 (20.0)
Hypocalcaemia	15 (33.3)	3 (12.5)	1 (20.0)
Rash pustular	7 (15.6)	0	0
AEs of relevance with an increased incidence of >10pp and a ≥2-fold difference in patients aged 12 to 16 years compared with patients aged ≥2 to 11 years, n (%)			
Dermatitis acneiform	12 (26.7)	23 (95.8)	5 (100)

Effect of gender

In the paediatric pool the incidence of SAEs, AEs leading to hospitalisation, AEs leading to treatment interruption and AESIs of Grade ≥3 were all higher for male patients, compared with female patients.

Effect of race

In SPRINT Phase II Stratum 1, AEs were reported for 42 patients who were White and 5 patients who were non-White, and in the paediatric pool, AEs were reported for 60 patients who were white and 9 patients who were non-White.

Immunological events

Not applicable

Safety related to drug-drug interactions and other interactions

See section 2.4.2 Pharmacokinetics.

Discontinuation due to adverse events

Dose interruptions and reductions due to adverse events were reported in 78% and 32% of patients, respectively.

Dose interruptions and reductions due to adverse events were reported in 78% and 32% of patients, respectively. The most commonly reported ADRs leading to dose modification (dose interrupted or dose reduced) of selumetinib were vomiting (26%), paronychia (16%), diarrhoea (15%) and nausea (11%). Permanent discontinuation due to adverse events was reported in 12% of the patients.

Overall, 6/14 (42.9%) AEs leading to treatment discontinuation were Grade 2, six (42.9%) were Grade 3 and two (14.3%) were Grade 4.

Of the AEs leading to treatment discontinuation, events of skin ulcer, MPNST, acute kidney injury (1 event), blood creatinine increased (2 events in 1 patient), and diarrhoea were reported as serious AEs.

In both SPRINT Phase II Stratum 1, and the paediatric pool, none AEs leading to permanent discontinuation of selumetinib were reported by more than 1 patient.

The majority (11/14 [78.6%]) of AEs leading to selumetinib discontinuation resolved after selumetinib was stopped, and for 3 AEs the outcome was unknown.

No new treatment-emergent AEs leading to permanent discontinuation of selumetinib were reported in the SPRINT Phase II Stratum 1 90 days updated safety report.

For the 6 patients who discontinued treatment in SPRINT Phase II Stratum 1, the total treatment duration ranged between 43 and 543 days. Of the 10 AEs that led to these 6 patients discontinuing, 2 were CTCAE Grade 2, 6 were CTCAE Grade 3, and 2 were CTCAE 4; 7 of these 10 AEs were SAEs.

Table 57: SPRINT Phase II Stratum 1 and the Paediatric pool: Adverse events leading to discontinuation of selumetinib, by system organ class and preferred term: (Safety analysis set)

	Number (%) of patients[a]					
MedDRA SOC and PT	Phase II Stratum 1 25 mg/m² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m² BID (N=56)	Phase I 20 mg/m² BID (N=12)	Phase I 25 mg/m² BID (N=6)	Phase I 30 mg/m² BID (N=6)	Paediatric pool All doses (N=74)
Patients with any AE leading to discontinuation[b]	6 (12.0)	6 (10.7)	1 (8.3)	0	2 (33.3)	9 (12.2)
Investigations	**2 (4.0)**	**2 (3.6)**	**0**	**0**	**0**	**2 (2.7)**
Blood creatinine increased	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Weight increased	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Gastrointestinal disorders	**1 (2.0)**	**1 (1.8)**	**1 (8.3)**	**0**	**1 (16.7)**	**3 (4.1)**
Diarrhoea	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Gastro-oesophageal reflux disease	0	0	1 (8.3)	0	0	1 (1.4)
Nausea	0	0	1 (8.3)	0	0	1 (1.4)
Stomatitis	0	0	0	0	1 (16.7)	1 (1.4)
Infections and infestations	**1 (2.0)**	**1 (1.8)**	**0**	**0**	**0**	**1 (1.4)**
Paronychia	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (2.0)**	**1 (1.8)**	**0**	**0**	**0**	**1 (1.4)**
Peripheral nerve sheath tumour malignant	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Renal and urinary disorders	**1 (2.0)**	**1 (1.8)**	**0**	**0**	**0**	**1 (1.4)**
Acute kidney injury	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Skin and subcutaneous tissue disorders	**1 (2.0)**	**1 (1.8)**	**0**	**0**	**0**	**1 (1.4)**
Skin ulcer	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
General disorders and administration site conditions	**0**	**0**	**0**	**0**	**1 (16.7)**	**1 (1.4)**
Fatigue	0	0	0	0	1 (16.7)	1 (1.4)
Musculoskeletal and connective tissue disorders	**0**	**0**	**0**	**0**	**1 (16.7)**	**1 (1.4)**
Myalgia	0	0	0	0	1 (16.7)	1 (1.4)

[a] Number (%) of patients with an AE leading to discontinuation, sorted in decreasing frequency of events in Phase II Stratum 1.

[b] Action taken, selumetinib permanently stopped.

Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.

Adverse events from other studies

▪ Early Access Program (EAP)

In the ongoing EAP, 166 patients (108 patients via named patient supply under Study D1346R00001 and 58 patients via US intermediate access protocol for Study D1346R00002) with NF1 and inoperable PN received selumetinib at a dose of 25 mg/m^2 BID (DCO 31 January 2019).

As part of the EAP, 273 AEs occurred in 75 patients and the nature of AEs reported was consistent with the safety profile of selumetinib in SPRINT Phase II stratum 1 and SPRINT phase I studies. In general, the type of AEs reported in the EAP were similar to the AEs reported in the clinical study. The majority of AEs were non-serious, with none life-treating or fatal events. SAEs that led to hospitalisation, included urinary tract infection, cellulitis, cystitis, dermatitis acneiform, gastrointestinal disorder, hallucination, and respiratory tract infection. The most commonly reported other SAEs included blood creatine phosphokinase increased and dermatitis acneiform, diarrhoea, and ejection fraction increased. Two serious cases of ejection fraction decreased were reported in paediatric patients aged of 6 and 11 years-old and for whom the event was considered related to selumetinib by the reporting physician. Selumetinib

treatment was discontinued. During the pivotal SPRINT Phase II stratum 1 and SPRINT phase I studies only asymptomatic left ventricular ejection fraction reductions were reported.

▪ Externally Sponsored Paediatric Studies (ESRs)

In the ongoing paediatric ESRs, 291 patients received selumetinib for a range of indications.

During these studies, 103 cases corresponding to 178 SAEs were reported. Out of these 178 SAEs, 21 events were considered life-threatening. However, the paediatric population of these studies (low grade glioma, multiply-relapsed paediatric) differs from NF1 patients, one cannot exclude that these events were precipitated by underlying diseases.

The most commonly reported SAEs included blood creatine phosphokinase increased, hydrocephalus, headache, rash maculo-papular, hyponatraemia, paronychia, pyrexia, vomiting, dehydration, abdominal pain, constipation, hypoxia, muscular weakness, optic nerve disorder, seizure, sepsis, suicidal ideation, and vision blurred. None of these SAEs had a fatal outcome. AEs that were considered as life threatening included blood creatine phosphokinase increased, agitation, anxiety, optic nerve disorders, sepsis, suicidal ideation, acidosis, apnoea, depressed level consciousness, hydrocephalus, hyperglycaemia, lipase increased, pulmonary haemorrhage, and pyrexia. These data were consistent with the safety profile of selumetinib.

Neither in EAP and ESRs studies fatal cases occurred.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The Applicant provided data from two main datasets: SPRINT II stratum 1 and paediatric pool.

Due to the small paediatric dataset, the evaluation of selumetinib has been completed by safety data from 7 studies in adult patients with cancer (n=347) including one phase III study (SUMIT). Furthermore, safety data from studies performed as part of the clinical pharmacology program (e.g. pharmacokinetic and drug-drug interactions studies) were also analysed although they had been performed in 380 healthy volunteers.

Additional studies, Early Access Program studies (EAP), and paediatric externally-sponsored studies (ESRs) have been also supplied.

The ages of the children at the enrolment ranged from 3 to 19 years (median 10.3 y; mean 10.5y) in the paediatric pool. Male represented 58.1% of the population. White subjects (87%) were the most presented patients. At baseline, prior medication was taken by 67.6 % of the patients and 59.5 % had prior surgery.

The median exposure time was 26.3 months in the SPRINT Phase II Stratum 1 study, with an additional 7.4 months duration of exposure at the moment of the 90 Days safety update analysis. Of the patients included in the Paediatric pool analysis, almost half (48.6%) were treated for more than 24 months. Although, the median treatment duration in the paediatric studies is considered quite long, patients might be treated even longer (up to many years) in real life. Furthermore, given the limited duration of follow-up, potential late effects of the treatment are not known.

The recommended dose for selumetinib is 25 mg/m^2 of body surface area (BSA), taken orally twice daily (BID; approximately every 12 hours). Dosing is individualised based on BSA (mg/m^2), and rounded to

the nearest achievable 5 mg or 10 mg dose, up to a maximum single dose of 50 mg. Selumetinib is not recommended in patients with a BSA <0.55 m^2.

In the event of toxicity, the following dose modifications are recommended:

Table 58: **Recommended dose reductions for adverse reactions**

Body surface area (BSA)	Initial Koselugo dose (mg/twice daily)	First dose reduction (mg/dose)		Second dose reduction (mg/dose)[a]	
		Morning	Evening	Morning	Evening
0.55 – 0.69 m^2	20 mg in the morning and 10 mg in the evening	10	10	10 once daily	
0.70 – 0.89 m^2	20	20	10	10	10
0.90 – 1.09 m^2	25	25	10	10	10
1.10 – 1.29 m^2	30	25	20	20	10
1.30 – 1.49 m^2	35	25	25	25	10
1.50 – 1.69 m^2	40	30	30	25	20
1.70 – 1.89 m^2	45	35	30	25	20
≥ 1.90 m^2	50	35	35	25	25

[a] Permanently discontinue treatment in patients unable to tolerate Koselugo after two dose reductions.

Table 59: Recommended dose modifications for adverse reactions

CTCAE Grade*	Recommended dose modification
Grade 1 or 2 (tolerable – can be managed with supportive care)	Continue treatment and monitor as clinically indicated
Grade 2 (intolerable – cannot be managed with supportive care) or **Grade 3**	Interrupt treatment until toxicity is grade 0 or 1 and reduce by one dose level when resuming therapy (see Table 63)
Grade 4	Interrupt treatment until toxicity is grade 0 or 1, reduce by one dose level when resuming therapy (see Table 63). Consider discontinuation

* Common Terminology Criteria for Adverse Events (CTCAE)

All of 74 patients in the paediatric pool experienced at least one dose interruption over their entire treatment duration. Most of the interruptions were caused by patient's compliance. Overall, 82.4% of patients experienced lack of compliance, but no correlation could be identified between lack of compliance, the reasons behind, and patient's age. There is no indication that difficulties with capsule intake resulted in more dose interruptions or decreased compliance for the youngest age group. Interruptions were mostly short and did not lead to substantial decrease of total treatment duration. Moreover, there was no clear indication of decreased efficacy in patients with frequent interruptions.

Some patients, in particular children < 6 years of age, may be at risk of choking on a capsule formulation due to developmental, anatomical or psychological reasons. Selumetinib should not be administered to patients who are unable or unwilling to swallow the capsule whole. Younger patients or those who may have difficulty swallowing a capsule should be assessed for their ability to swallow a capsule before starting treatment. There are no specific techniques required to swallow selumetinib capsules. Standard medicine swallowing techniques may help patients. Referral to an appropriate health care professional such as a speech and language therapist should be considered if patients are unable to swallow a capsule to identify suitable methods that can be tailored to the particular patient need (see sections 4.2 and 4.4 of the SmPC).

The risk of choking related to the size of the capsule has been added in the safety concerns of the RMP as an important potential risk and will be further investigated in the context of the non-interventional PASS (see SOB). The applicant is developing an age appropriate formulation and is expected to provide a status update in the context of the annual renewals.

AEs were usually mild or moderate in severity and were managed by either dose modification with or without additional intervention (symptomatic and/or supportive treatments) enabling the patients to be on selumetinib treatment for long periods of time.

In the paediatric pool, the most frequently observed ADRs by Preferred terms (PTs) that characterise selumetinib safety profile were: vomiting (82%), rash (80%), blood creatine phosphokinase increased (76%), diarrhoea (77%), nausea (73%), asthenic events (59%), dry skin (58%), pyrexia (57%), acneiform rash (54%), hypoalbuminaemia (50%), aspartate aminotransferase increased (50%) and paronychia (45%). Dose interruptions and reductions due to adverse events were reported in 78% and 32% of patients, respectively.

Despite the toxicity profile of selumetinib, treatment duration for most of the patients was quite long, indicating that the ADRs were manageable for patients.

In paediatric pool, 57/74 and 61/74 patients experienced diarrhoea and vomiting, respectively, and among those 11 and 6 patients experienced CTCAE Grade ≥ 3, respectively. Other cases were mostly CTCAE Grade ≤2 and are described as ADRs in section 4.8 of the SmPC.

Although the reason (pathophysiology) is not completely understood, a higher incidence of AEs of diarrhoea, nausea, vomiting, and fatigue was reported in the first year compared to subsequent years. This was the case for both Grade 1-2 events (majority of the cases) as for Grade 3 events. Only 3 patients discontinued treatment due to one of these common AEs.

AEs of nausea, vomiting, and diarrhoea were in most cases managed either with no medication or with symptomatic treatment, which included anti-emetics (for nausea and vomiting) and loperamide (for diarrhoea).

If vomiting occurs after selumetinib is administered, an additional dose is not to be taken. The patient should continue with the next scheduled dose.

Two events of diarrhoea in 2 patients were managed with supportive treatment (defined as medications and/or IV fluids and/or blood products), which consisted of sodium chloride and potassium chloride fluids.

A total of 4 patients had an AE of weight increased. The compatible time to onset with selumetinib, including one with a positive dechallenge, having temporarily needed interruption of selumetinib treatment and adjusted dose for resolving, show a trend of pattern for this AE. No signal emerged from non-clinical data as regards weight increased. Based on the available data, no firm conclusion can be drawn regarding the causal association of weight increased to selumetinib and it is therefore not considered as an ADR. This adverse event should be monitored through routine pharmacovigilance.

Recurrent AEs were reported, including patients who experienced more than 10 events for one of the AEs. Most of these recurrent events were low-grade and did not lead to treatment discontinuation. Although not measured, it can be expected that these frequent recurring or long-lasting AEs have a negative effect on quality of life of these individual patients.

Most AEs could be adequately managed with dose interruptions (78% of patients had an AE leading to dose interruption) and dose reductions (32%).

To study the impact of treatment holidays to manage AEs on treatment efficacy, a longitudinal analysis was conducted (data not shown). Effect of prolonged dose interruption (cumulative interruptions [can be consecutive or not consecutive] of > 28 days between 2 assessments) and/or dose reductions on PN

tumour volume change, was analysed. Based on this limited dataset it appears that dose interruption for prolonged periods may have greater impact on efficacy than dose reduction. Therefore, the use of formal treatment holidays is not recommended.

Adverse reactions of blurred vision have been reported in paediatric patients receiving selumetinib. Isolated cases of RPED, CSR and RVO in adult patients with multiple tumour types, receiving treatment with selumetinib monotherapy and in combination with other anti-cancer agents, and in a single paediatric patient with pilocytic astrocytoma on selumetinib monotherapy, have been observed. Patients should be advised to report any new visual disturbances. In line with clinical practice an ophthalmological evaluation prior to treatment initiation and at any time a patient reports new visual disturbances is recommended. In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmic assessment should be conducted every 3 weeks until resolution. If RPED or CSR is diagnosed and visual acuity is affected, selumetinib therapy should be interrupted and the dose reduced when treatment is resumed. If RVO is diagnosed, treatment with selumetinib should be permanently discontinued (see sections 4.2, 4.4 and 4.8 of the SmPC).

The risks of RVO, CSR and RPED are considered as potential important risks in the RMP (see section on Risk Management Plan).

One grade 1 case of cataract related to selumetinib was reported in SPRINT phase II stratum 1 and two cases of eye disorders were recorded as part of the Early Access Program. No firm conclusion can be drawn regarding the causal association to selumetinib. Cataract and eye disorders should however be monitored through routine pharmacovigilance.

Asymptomatic decreases in ejection fraction have been reported in 22% of paediatric patients in the pivotal clinical study. Median time to initial onset of these adverse reactions was 226 days. A small number of serious reports of LVEF reduction associated with selumetinib have been reported in paediatric patients who participated in an expanded access program.

Paediatric patients with a history of impaired left ventricular function or a baseline LVEF below institutional lower level of normal (LLN) have not been studied. LVEF should be evaluated by echocardiogram before initiation of treatment to establish baseline values. Prior to starting selumetinib treatment, patients should have an ejection fraction above the institutional LLN. LVEF should be evaluated at approximately 3 month intervals, or more frequently as clinically indicated, during treatment. Reduction in LVEF can be managed using treatment interruption, dose reduction or treatment discontinuation. In cases of asymptomatic LVEF reduction of ≥ 10 percentage points from baseline and below the institutional LLN, selumetinib treatment should be interrupted until resolution. Once resolved, selumetinib should be reduced by one dose level when resuming therapy.

In patients who develop symptomatic LVEF reduction or a grade 3 or 4 LVEF reduction, selumetinib should be discontinued and a prompt cardiology referral should be carried out (see sections 4.2, 4.4 and 4.8 of the SmPC).

The risk of LVEF reduction is included in the RMP as an important identified risk (See RMP).

Cases of oedema have been reported and this AE should be monitored through routine pharmacovigilance to further understand if the emerging body of data could provide insights to better characterise the pathophysiology of this AE in paediatric patients with NF1.

Further to the bone effects identified in rats, the Applicant carried out a comparison of the growth of patients enrolled in the paediatric pool in comparison with patients in the Natural History cohort (external control) based on the WHO growth charts (developed for children at birth to five years of age). Results (data not shown) indicate homogeneous distribution of the growth between paediatric population of NF1 from SPRINT Phase I and II studies with those from the Natural History cohort. However, considering

that these data are based on a prediction, the conclusion of which should be interpreted with caution, and considering the limited number of patients included in the clinical trials, the risk of physeal dysplasia cannot be ruled out and constitutes a potential concern in this patient population. Therefore, physeal dysplasia has been added as an important potential risk in the RMP and this risk will be monitored as part of the planned non-interventional PASS (see section "Risk management Plan").

Skin rash (including maculopapular rash and acneiform rash), paronychia and hair changes have been reported very commonly in the pivotal clinical study. Pustular rash, hair colour changes and dry skin were seen more frequently in younger children (age 3-11 years) and acneiform rash was seen more frequently in post-pubertal children (age 12-16 years) (see sections 4.4 and 4.8 of the SmPC).

The data provided from the EAP and ESR were of low quality. It is therefore not possible to compare the safety data from the EAP and ESR with the safety results of the clinical study although it is agreed that no specific trend or pattern is seen from these studies that would suggest a safety signal.

In this population, serious adverse events were reported in 17/74 patients. The following serious adverse reactions were reported: diarrhoea (3%), anaemia (3%) pyrexia (3%), blood CPK increased (3%), blood creatinine increased (1%). Eleven (11) out of 17 patients were hospitalized. Most of them recovered. For 4 patients, the SAE led to permanent discontinuation of selumetinib and for another one who experienced a humerus fracture the outcome was unknown at the 90 DSU DCO. No death occurred in paediatric patients.

Patients should be advised not to take any supplemental vitamin E. Koselugo 10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS). Koselugo 25 mg capsules contain 36 mg vitamin E as TPGS. High doses of vitamin E may increase the risk of bleeding in patients taking concomitant anticoagulant or antiplatelet medicinal products (e.g., warfarin or aspirin). Anticoagulant assessments, including international normalized ratio or prothrombin time, should be conducted more frequently to detect when dose adjustments of the anticoagulant or antiplatelet medicinal products are warranted (see sections 4.4 and 4.5 of the SmPC).

Liver laboratory abnormalities, specifically AST and ALT elevations, can occur with selumetinib. Liver laboratory values should be monitored before initiation of selumetinib and at least monthly during the 6 first months of treatment, and thereafter as clinically indicated. Liver laboratory abnormalities should be managed with dose interruption, reduction or treatment discontinuation (see sections 4.2, 4.4 and 4.8 of the SmPC).

The risk of hepatotoxicity is included in the RMP as a potential important risk.

Haematuria and proteinuria occurred in more than 20% of patients. However no causal relationship could be identified. These adverse events will be monitored through routine pharmacovigilance.

No causal relationship with selumetinib could be established for the reported events of calcaemia, glycaemia, kalaemia, magnesaemia, natraemia and amylase increased. However, the monitoring of these AEs should be pursued through routine pharmacogivilance.

Age, gender or race did not raise particular safety issues.

There are no data on the use of selumetinib in pregnant women. Studies in animals have shown reproductive toxicity including embryofoetal death, structural defects and reduced foetal weights. Koselugo is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Koselugo. It is recommended that a pregnancy test should be performed on women of childbearing potential prior

to initiating treatment. Both male and female patients (of reproductive potential) should be advised to use effective contraception during and for at least 1 week after completion of treatment with Koselugo.

If a female patient or a female partner of a male patient receiving Koselugo becomes pregnant, she should be apprised of the potential risk to the foetus.

It is not known whether selumetinib, or its metabolites, are excreted in human milk. Selumetinib and its active metabolite are excreted in the milk of lactating mice. A risk to the breast-fed child cannot be excluded, therefore breast-feeding should be discontinued during treatment with Koselugo.

There are no data on the effect of Koselugo on human fertility. Selumetinib had no impact on fertility and mating performance in male and female mice, although a reduction in embryonic survival was observed in female mice (see sections 4.4, 4.6 and 5.3 of the SmPC).

There is no specific treatment for overdose. If overdose occurs, patients should be closely monitored for signs and symptoms of adverse reactions and treated supportively with appropriate monitoring as necessary. Dialysis is ineffective in the treatment of overdose (see section 4.9 of the SmPC). The risk of overdose should be closely monitored through routine pharmacovigilance.

No studies on the effects on the ability to drive and use machines have been performed. Koselugo 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 machines (see section 4.7 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

Upon request from the CHMP, an ad hoc expert group meeting (AHEG) was convened on 9 February 2021. The AHEG answers to the CHMP questions on safety aspects are as follows:

1. **Is the safety profile as observed thus far acceptable for the target population.**

   The data submitted as part of the application indicate an overall manageable toxicity for the observed exposure. However, caution is warranted, especially for cardiac toxicity and long-term safety especially in young patients. Although there are no specific concerns based on the available data, special caution and specific and sensitive monitoring should be implemented to detect any possible toxicity and consequences on development.

2. **Are there concerns about long term safety. If so, which?**

   There are no specific concerns, however, in given the limited duration of follow-up, and especially in the vulnerable population of younger children, special caution is recommended to monitor cardiotoxicity and any developmental issues (see above).

3. **What, if any, type of further clinical data would be required post-approval?**

   It was agreed that long-term efficacy and impact on NF and safety data should be collected as extensively and rapidly as possible, and periodically assessed since the current follow-up is relatively short.

   Concerning efficacy, this should include clinical assessment (including motor activity, pain, cosmetic improvement, and PROs).

Concerning safety, the data collection should use specific and sensitive methods to detect any possible toxicity and consequences on development, in particular cardiac, skeletal, and neurologic development including cognitive development, as appropriate in the younger population.

In term of study design, a randomised trial could of course address important questions although feasibility in this rare disease is questioned. Concerning treatment duration and schedule optimisation, there was a suggestion that a randomised controlled trial with a cross-over design could be conducted to inform on potential treatment patterns (continuous versus intermittent depending on progression) that could improve the outcome, including quality of life. However, again, feasibility was questioned.

A more likely feasible design would be an observational study or a registry to address both efficacy and safety aspects, as well as treatment duration, treatment interruptions and reasons, subsequent treatments.

Further development to assess efficacy/safety in younger children is also recommended.

4. **Are the currently available pharmaceutical form (capsule and its size) and the measures proposed to enhance treatment compliance and prevent choking acceptable for the target population (i.e. paediatric patients aged 3 years and above)?**

   It was agreed that the currently available pharmaceutical form is far from optimal due to especially its size (regardless of the age of the patient), and that it may constitute a prohibitive risk in patients for whom adequate choking prevention is not feasible.

Additional safety data needed in the context of a conditional MA

In order to address the uncertainties related to the limited safety data set and the long-term effects of selumetinib administered to a paediatric patient population, the applicant will submit the following data as specific obligations.

- Safety data from a real-world post-authorisation safety study (PASS) is planned to include a baseline, retrospective, cross-sectional cohort comprising approximately 125 NF1 patients in the EU with symptomatic, inoperable PN who have been prescribed at least one dose of selumetinib and who are aged 3 to ≤18 years at the start of selumetinib treatment. From this study population, a nested prospective cohort of approximately 100 patients aged ≥8 years old (and prior to attainment of Tanner Stage V [sexual maturity rating]) will be followed prospectively.

- Efficacy and safety data from the pivotal SPRINT Phase II Stratum 1 with longer follow-up. At the original DCO (29-Jun-2018) the median duration of selumetinib treatment in SPRINT Phase II Stratum 1 was 2.2 years (range 0.1 to 2.9 years). A second (unplanned) DCO on 31-Mar-2021 will provide 2 years and 9 months of further data. This would more than double the median follow-up.

- Supportive efficacy and safety data from SPRINT Phase I with longer follow-up. At the original DCO (29-Jun-2018) the median duration of selumetinib treatment in SPRINT Phase I was 4.4 years (range 0.4 to 5.9 years). A second DCO on 27-Feb-2021 will provide 2 years 8 months of further data. This would thus extend the total follow-up to 6-7 years.

2.6.2. Conclusions on the clinical safety

The assessment of selumetinib clinical safety is based on data from 74 paediatric patients enrolled in the two pivotal studies SPRINT phase I (n=24) and SPRINT phase II (n=50), with NF1 PN who received selumetinib monotherapy (20-30 mg/m² twice daily). The median total duration exposure was 28 months. The ages of the children at the enrolment ranged from 3 to 19 years.

Most of the AEs were mild or moderate however two-thirds of patients had an AE of grade ≥3 mainly: diarrhoea, blood creatine phosphokinase increased, paronychia, pyrexia and vomiting. Furthermore, drug interruptions due to AEs were observed in more than three-quarter of paediatric patients occurring as early as grade 2. Therefore, selumetinib cannot be considered as a well-tolerated drug in this population. The incidence of SAEs in the paediatric pool was 23%.

A high rate of temporary dose interruptions due to the lack of compliance was observed in more than 80% of patients and 77% stopped due to adverse events.

Due to the large size of the capsule, there is a risk of choking in young patients, notably those under 6-years old (see RMP). The applicant is developing an age-appropriate formulation and is requested to provide a status update in the context of the annual renewals.

There are remaining uncertainties regarding the risk of physeal dysplasia which will be addressed in the context of the non-interventional PASS (see SOB).

The overall safety data for selumetinib show adverse drug reactions consistent with the known safety profile of MEK 2 inhibitors (e.g. binimetinib, trametinib).

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

Non-interventional post-authorisation safety study (PASS): in order to confirm the long-term safety of selumetinib in the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above, the applicant will conduct and submit the results of a non-interventional PASS comprising approximately 125 NF1 patients in the EU who have been prescribed at least one dose of selumetinib and who are aged 3 to ≤18 years at the start of selumetinib treatment. A nested cohort of approximately 100 patients aged ≥8 years old (and prior to attainment of Tanner Stage V [sexual maturity rating]) will be followed prospectively. The clinical study report will be submitted by 31 December 2027:

2.7. Risk Management Plan

Safety concerns

Table 60: **Summary of the safety concerns:**

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

Pharmacovigilance plan

Table 61: **Ongoing and planned additional pharmacovigilance activities**

Category 3 - Required additional pharmacovigilance activities				
Study 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. Status Planned.	Summary of objectives To characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice.	Safety concerns addressed LVEF reduction Physeal dysplasia Ocular toxicity Myopathy Hepatotoxicity Long term exposure (including long term safety data on developmental toxicity in children)	Milestones for EMA Protocol submission Final report	Due dates for EMA Within 3 months of authorisation. Estimated Q4 2027.

Risk minimisation measures

Routine risk minimisation measures are considered sufficient to minimise the risks of the product.

Table 62: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Left ventricular ejection fraction reduction (important identified risk)	Routine risk communication: SmPC Section 4.2, 4.4, 4.8. Routine risk minimisation activities recommending specific clinical measures: SmPC Section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of LVEF reduction.
Physeal dysplasia (important potential risk)	None.
Ocular toxicity (important potential risk)	Routine risk communication: SmPC Section 4.2, 4.4 and 4.8 (ADR of RVO, RPED and CSR reported in adult patients with multiple tumour types, but not reported in SPRINT Phase II Stratum 1). Routine risk minimisation activities recommending specific clinical measures: SmPC Section 4.4

Safety concern	Routine risk minimisation activities
	Guidance is provided for monitoring and management (interrupting or stopping treatment) of events.
Myopathy (important potential risk)	There are no routine risk minimisation activities for myopathy. Routine risk communication for CPK increases, which may be a precursor for the clinical outcome of myopathy is outlined below: SmPC Section 4.8.
Hepatotoxicity (important potential risk)	There is no routine risk communication for hepatotoxicity. Routine risk communication for ALT and AST increases that may be precursors for the clinical outcome of hepatotoxicity is outlined below: SmPC Section 4.8. Routine risk minimisation activities recommending specific clinical measures: SmPC Section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of ALT and AST increases.
Choking on the capsule (important potential risk)	Routine risk communication: SmPC Section 4.2 under the subheading 'Method of administration' and Section 4.4. Routine risk minimisation activities recommending specific clinical measures: SmPC Section 4.2 Guidance is provided for patients with difficulties swallowing capsules.
Long term exposure (including long term safety data on developmental toxicity in children [Missing Information])	None.

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

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

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 10.04.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of selumetinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers selumetinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

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

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Koselugo (selumetinib) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It has a PASS imposed at the time of authorisation; [REG Art 9(4)(cb), DIR Art 21a(b];
- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

3.1.2. Available therapies and unmet medical need

Currently there is no approved medical treatment in the EU to cure, prevent, or reduce the volume of PNs. The only available options to treat and manage NF1 are pain management and surgical excision to

remove as much of the PN as possible. However, for many patients surgery is not a viable option as most PN are not amenable to complete resection due to encasement of, or close proximity to, vital structures. Furthermore, complete resection is difficult to achieve, with a high risk of iatrogenic injury to related nerves and surrounding soft tissues and haemorrhage due to the invasiveness or high vascularity of the PN. Following subtotal or partial PN resection, 18% of patients experienced permanent surgical complications, including speech abnormalities, nerve palsies, and pain, and 55% of patients experienced PN regrowth. Furthermore, incompletely resected PN tend to regrow after surgery.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is from a single phase I/II (SPRINT) open-label, single-arm, multi-centre Phase I/II study that aimed to evaluate the safety, tolerability, and efficacy of selumetinib in paediatric patients with NF1 and inoperable PN (defined as PN that cannot be surgically completely removed without risk of substantial complications due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN).

The target PN, the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was evaluated for response rate using volumetric magnetic resonance imaging (MRI) analysis per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria.

Supportive efficacy and safety data were provided from the Phase I of the SPRINT study in which patients received selumetinib at doses of 20, 25 and 30 mg/m^2 BID (Dombi et al. 2016).

The Applicant also provided External Control Data (reported in SPRINT Phase II Stratum 1 Clinical Study Report) from an NCI POB NF1 Natural History study (age-matched cohort for primary analysis and contextualisation of SPRINT data) and the Placebo arm of tipifarnib Study 01-C-0222.

3.2. Favourable effects

In the study SPRINT Phase I/II, a total of 50 paediatric patients with NF1 and PN were included. The time of data cut-off for the results is 29-Jun-2018, at which timethe DCO the median follow-up time was 24 cycles.

The ORR on the target tumour volume according to the REiNS criteria [Dombi et al. 2013], was 66.0% (95% IC 51.2, 78.8) based on NCI POB analysis by a single reviewer. No patients had a complete response, 33 (66.0%) patients had a confirmed PR (i.e. volume decrease ≥ 20% confirmed within 3 to 6 months after first response), 4 patients (8.0%) had an unconfirmed PR and 11 (22%) had stable disease (volume change < 20%), and no patients had a progression. Two patients did not participate to this evaluation due to the absence of post baseline MRI scan.

The ORR per (pre-planned) first ICR sensitivity analysis was 44.0% (95% CI: 30.0, 58.7). Per post-hoc second ICR analysis the ORR was 40.0% (95% CI: 26.4, 54.8), and the resulting average ICR was 40.0% (95% CI: 30.0, 58.7).

Median duration of response (DOR) was not reached. The number (percentage) of patients remaining in (confirmed) response after 12 and 24 cycles was 29 (87.9%) and 9 (27.3%), respectively.

Median progression free survival (PFS) and time to progression (TTP) (no patient died) was not reached (with a median follow-up for PFS of 24.0 cycles). The median time to onset of response was 7.2 months (range 3.3 months to 1.6 years). The median (min-max) time to the maximal PN shrinkage from baseline was 14.6 months (3.3 months to 2.7 years).

In the SPRINT Phase II Stratum 1, the median PN volume change per year observed was -10.2% (range -27.3% to 19.0%). The median best percentage change from baseline in target PN volume was -27.85%.

The influence of pain on daily functioning showed a trend over improvement in the score which was mainly supported by the scores reported by the parents. The correlation between shrinking tumour and PII was weak. Effect on tumour reported pain and global pain was also assessed by the GIC, individually some improvement was observed.

The effect on mobility was assessed using self-PROMIS, a reported and parent reported PROMIS score. A positive trend was reported as rated by parents but not for self-evaluation. For mobility, the correlation between the change in PROMIS and change in target PN volume was weak for self-reported score and moderate for parent reported score. On the contrary, the correlation was moderate for self-reported score and weak for parent reported score regarding upper extremity score.

3.3. Uncertainties and limitations about favourable effects

The sample size of the pivotal study SPRINT Phase II stratum 1 is limited (n=50) and there is a great heterogeneity of the population in terms of location of the target PN and comorbidities.

The pivotal study had a single-arm design and thus lacking an internal control. The comparison to the external controls provided to contextualise the data was merely of a descriptive nature and hampered by differences between the design of the studies, regarding e.g. eligibility criteria, baseline demographic and disease characteristics, and timing of imaging. Furthermore, there is a potential subjectivity in the assessment of the imaging data in the external control studies as data have not been assessed by ≥2 independent readers who were blinded for patient exposition and time point, also avoiding sequential presentation of images from the same patient (via random presentation), as was recommended in the protocol assistance (PA). The results are however accepted.

3.4. Unfavourable effects

The most common adverse reactions of any grade (incidence ≥ 45%) were vomiting (82%), rash (80%), blood creatine phosphokinase increased (76%), diarrhoea (77%), nausea (73%), asthenic events (59%), dry skin (58%), pyrexia (57%), acneiform rash (54%), hypoalbuminaemia (50%), aspartate aminotransferase increased (50%) and paronychia (45%).

The most commonly reported ADRs of CTCAE Grade ≥3, by PTs were: diarrhoea (15%), blood CPK increase (9%), paronychia (9%), vomiting (8%), pyrexia (8%) and rash (5%).

3.5. Uncertainties and limitations about unfavourable effects

The safety data on selumetinib in the treatment of NF1 is limited to 74 paediatric patients.

There is a risk of choking in young patients because of the large capsule. An age-appropriate formulation is currently under development and the applicant will provide a status update in the context of annual renewals (see RMP)

the effect of long term exposure and the long term toxicity on the development of children (physeal dysplasia) is unknown. These issues will be further investigated in the context of a non-interventional PASS study (see SOB).

3.6. Effects Table

Table 68: Effects Table for Kolesugo for the treatment of neurofibromatosis type 1 (NF1) symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients aged 3 years and above (data cut-off: 28/06/2018).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Decrease tumour size	ORR	%	66	N/A	Uncontrolled study Primary endpoint First ICR ORR: 44 % Second ICR ORR : 40% Average ICR ORR : 44%	SPRINT phase II
	DOR DoR ≥ 12 months	Cycle n (%)	Median not reached 27 (82%)			
COAs	Pain Motor function Visual dysfunction Bowel and bladder function Disfigurement Quality of life		Some effect at an individual level.		No statistical correlation between tumour reduction and COAs	
Unfavourable Effects* **From** Pooled paediatric data (Sprint phase II stratum 1 + Sprint phase I)						
Grade 3-4 AEs		%	67.6	N/A	No comparator. Selumetinib causal relationship based on the investigator appreciation.	
SAEs			23.0			
AEs leading to discontinuation			12.2			
Vomiting*			8,1			
Blood CPK increased*			9,5			
Diarrhoea*			14,9			
Pyrexia*			8,1			
Paronychia *			9,5			
Anaemia*			2,7			

Abbreviations: SEL= selumetinib

Note: *only grade ≥3 AE are displayed

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is currently no approved medical therapy for the treatment of symptomatic, inoperable PNs in the EU, and there is thus an unmet medical need.

The highest reported effect was the 66% objective response rate (33 patients) in the pivotal study SPRINT phase II study, when assessed by NCI POB Central analysis (versus 44% when reanalysed by a first Independent Central Review, 40% by a second ICR, and 44% for the average ICR). All 33 patients had a confirmed partial response (defined as volume decrease ≥20%) as best response and none of the 50 enrolled patients experienced progression.

Considering that the natural course of PNs is growth or at best stay stable over time, the observed decrease of tumour volume and the absence of progression in the pivotal study can in principle be attributed to selumetinib.

Regarding clinical outcomes, some improvements were observed, however the open-label trial design limits interpretability of those endpoints as patient's and parent's knowledge of treatment assignment may lead to an overestimation of treatment effect.

While the data have not shown a statistical correlation between the ORR and the clinical outcomes assessments, the AHEG considered that efficacy was shown for the duration of the pivotal trial (i.e. 2

years) as it is plausible that decrease of PN volume is associated with a decrease in symptoms/morbidity. Efficacy is therefore considered established.

The toxicity profile of Koselugo treatment is not considered mild, incidence of the grade 3 AEs are considerable, and recurring events are reported that might impact patients' quality of life. However, most toxicity seemed to be manageable (with treatment interruptions, dose reduction or supportive care) in this particular paediatric population, and long-term treatment is tolerated by most of the patients. Taking into account the burden of the disease, the safety profile is acceptable. However, to address the uncertainties on long-term safety, the applicant will conduct a PASS.

The proposed formulation is a hard capsule which is not considered appropriate for younger patients because of its size; this is considered to represent a risk as some patients will have difficulties with the intake of the capsules. Treating physicians should propose standard swallowing techniques. For patients who have difficulties swallowing the capsule, referral to an appropriate health care professional such as a speech and language therapist could be considered to identify suitable methods that can be tailored to the particular patient. For children who are not able or who opposes to taking the capsules, treatment should not be persevered or started.

An age appropriate formulation is currently being developed by the MAH and is a binding measure in the paediatric investigation plan. The MAH should report on the progress of the development of this age-appropriate formulation in the context of the annual renewals.

3.7.2. Balance of benefits and risks

The observed responses and the absence of progression (as best response) can in principle be attributed to selumetinib. The exact effect size of selumetinib treatment on PN volume/growth rate remains unknown, although an ORR in the range of 40.0-66.0% may be assumed albeit with CIs extending from 26.4% to 78.8%.

It is plausible that a decrease in PN volume is associated with a decrease in symptoms, but a clear correlation has not been shown between PN shrinkage and the clinical outcome assessments used as measures for patient benefit at the population level. Despite the limitations of the pivotal study, clinical benefit was reported at the patient level by either the Investigator, the patient, or the patient's parents.

Three-quarters of doses interruptions were related to AEs, i.e. 58/74 patients (77%), approximately two-thirds of patients had an AE of grade ≥3 and serious adverse events were experienced by 23% of patients. Furthermore a potential risk of physeal dysplasia cannot be excluded. However, most toxicity seemed to be manageable (with treatment interruptions, dose reduction or supportive care) in this particular paediatric population. Taking into account the burden of the disease and the benefit to some patients, the safety profile is acceptable. However, to address the uncertainties on the long-term safety and the potential effect on the development of children, the applicant will conduct and submit a non-interventional PASS.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant who requested consideration for its application for a conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning

conditional marketing authorisations, as it aims at the treatment of a seriously debilitating disease. In addition, the product is designated as an orphan medicinal product.

PNs typically grow along large nerves and plexuses and are present at birth. PN manifestations vary and may continue to become apparent through late adolescence and early adulthood. Typical PNs are clinically distinct from localised (or 'nodular' or 'atypical') neurofibromas in that they can have complex shapes and sometimes reach very large size, with some documented as being 20% of body weight. 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. They have potential for malignant transformation and are considered by some to be pre-malignant.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive. When considering ORR in the context of improved clinical outcomes at the patient level, efficacy of selumetinib in patients with NF1 PN can be considered established, at least for the duration of follow-up of the pivotal trial (about 2 years). Furthermore, considering the burden of the disease, the safety profile is acceptable.
- It is likely that the applicant will be able to provide comprehensive data. The following specific obligations (SOBs) are agreed:

  - Efficacy and safety data from the pivotal SPRINT Phase II Stratum 1 with a longer follow-up. At the original DCO (29-Jun-2018) the median duration of selumetinib treatment in SPRINT Phase II Stratum 1 was 2.2 years (range 0.1 to 2.9 years). A second (unplanned) DCO on 31-Mar-2021 that will provide 2 years and 9 months of further data. This would more than double the median follow-up.

  - Supportive efficacy and safety data from SPRINT Phase I with a longer follow-up. At the original DCO (29-Jun-2018) the median duration of selumetinib treatment in SPRINT Phase I was 4.4 years (range 0.4 to 5.9 years). A second DCO on 27-Feb-2021 that will provide 2 years 8 months of further data. This would thus extend the total follow-up to 6-7 years.

  - Safety data from a non-interventional post-authorisation safety study (PASS). The PASS patient population is planned to include a baseline, retrospective, cross-sectional cohort comprising approximately 125 NF1 patients in the EU with symptomatic, inoperable PN who have been prescribed at least one dose of selumetinib and who are aged 3 to ≤18 years at the start of selumetinib treatment. From this study population, a nested prospective cohort of approximately 100 patients aged ≥8 years old (and prior to attainment of Tanner Stage V [sexual maturity rating]) will be followed prospectively.
- Unmet medical needs will be addressed, as there is currently no approved medical therapy for the treatment of symptomatic, inoperable PNs in the EU.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Since no treatment is available to treat patients with NF1 PN, the benefits to public health of the immediate availability of Koselugo is considered to outweigh the risks.

3.8. Conclusions

The overall B/R of Koselugo in the treatment of symptomatic, inoperable plexiform neurofibromas (PN)

in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above is positive subject to the specific obligations and conditions imposed as part of the conditional marketing authorisation granted.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Koselugo is favourable in the following indication:

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

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

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.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above, the applicant will submit the results from a longer follow-up of patients from study SPRINT Phase II Stratum 1 with a data cut-off of 31 March 2021. The clinical study report will be submitted by:	31/03/2022
In order to confirm the efficacy and safety of selumetinib in the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above, the applicant will submit the results from a longer follow-up of patients from study SPRINT Phase I with a data cut-off of 27 February 2021. The clinical study report will be submitted by:	31/03/2022
Non-interventional post-authorisation safety study (PASS): in order to confirm the long-term safety of selumetinib in the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 3 years and above, the applicant will conduct and submit the results of a non-interventional PASS in patients with NF1 who have been prescribed at least one dose of selumetinib and who are aged 3 to $\leqslant$18 years at the start of selumetinib treatment. A nested cohort of patients aged $\geqslant$8 years old (and prior to attainment of Tanner Stage V [sexual maturity rating]) will be followed prospectively. The clinical study report will be submitted by:	31/12/2027

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that selumetinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0279/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.