EU RMP	
Drug substance	Selumetinib
EMA version number:	4.0
AZ version number	4
AZ succession number	1
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Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for KOSELUGO™ (SELUMETINIB)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, Anne Lappereau-Gallot, as delegated by the QPPV in the EU.

Administrative information

Rationale for submitting an updated RMP:

The RMP update includes extended indication to adult patients with neurofibromatosis type 1 (NF1)-related plexiform neurofibroma (PN).

The RMP update includes:

- new granules in capsule pharmaceutical form of the medicinal product
- extended indication to paediatric patients from 1 year of age
- removal of important potential risk: choking on capsule.

Summary of significant changes in this RMP

The summary of significant changes proposed in the current RMP v4 is provided below.

Part I

Product(s) overview was amended in line with the proposed extended indication of the adult patients.

Part II SIII

Module SIII was revised to present the exposure data from the pivotal KOMET study and the NF1-PN adult capsule pool.

Part II SVII

Section 2.7.3 was updated in line with the data collected for the updated NF1-PN adult capsule pool.

Part III

Table of the planned and ongoing post-authorisation safety studies (PASSs) in Section 3.3 was revised to correct the PASS categorisation and update the milestone dates. These changes are also reflected in Annex 2.

Part VI

Changes introduced to the body of document were reflected in Part VI of the RMP, as applicable.

The summary of significant changes proposed in the RMP v3, undergoing assessment in parallel within a procedure EMEA/H/C/005244/X/0018/G, in comparison to the approved RMP v2 is provided below.

Part I

Product(s) overview was amended in line with the proposed changes in the pharmaceutical form of granules in capsule for opening and the extended indication of the paediatric patients from 1 year of age.

Part II SIII

Module SIII was revised to present the exposure data from the SPRINKLE study conducted in the paediatric population with neurofibromatosis type 1-related plexiform neurofibroma and the granule form of the product. The supporting paediatric pool was updated.

Part II SVII and SVIII

The important potential risk of choking on the capsule is removed from the list of safety concerns for KOSELUGO.

Section 2.7.3 was updated in line with the data collected for the updated paediatric pool and the SPRINKLE study.

Part III

Table of the planned and ongoing post-authorisation safety studies (PASSs) in Section 3.3 was revised to correct the PASS categorisation and update the milestone dates. These changes are also reflected in Annex 2.

Part VI

Changes introduced to the body of document were reflected in Part VI of the RMP, as applicable.

Other RMP versions under evaluation	**RMP version number:** 3 **Submitted on:** 22 November 2024 **Procedure number:** EMEA/H/C/005244/X/0018/G
Details of currently approved RMP	**Version number:** 2 **Approved within procedure**: EMEA/H/C/005244/R/0010 **Date of approval:** 31 May 2023

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BID	Twice daily
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum plasma concentration
CPK	Creatine phosphokinase
CSR	Central serous retinopathy (chorioretinopathy)
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular signal related kinase
EU	European Union
EU RMP	European Union Risk Management Plan
GI	Gastrointestinal
ILD	Interstitial lung disease
INN	International non-proprietary name
IOP	Intraocular pressure
LV	Left ventricular
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MHRD	Maximum human recommended dose
MRI	Magnetic resonance imaging
NF1	Neurofibromatosis type 1
NYHA	New York Heart Association
PASS	Post-authorisation safety study
PN	Plexiform neurofibroma

Abbreviation/ Special term	Definition/Explanation
PT	Preferred term (of MedDRA)
RMP	Risk Management Plan
RPED	Retinal pigment epithelial detachment
RVO	Retinal vein occlusion
SmPC	Summary of Product Characteristics
VEGF	Vascular endothelial growth factor

1. PART I: PRODUCT(S) OVERVIEW

Table 1-1 Product(s) overview

Active substance(s) (INN or common name)	Selumetinib
Pharmacotherapeutic group(s) (ATC code)	L01EE04
Marketing Authorisation Holder	AstraZeneca AB
Medicinal products to which this RMP refers	2
Invented name(s) in the EEA	KOSELUGO
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Non adenosine triphosphate-competitive MEK inhibitor
	Summary of mode of action: MEK proteins are components of the ERK pathway, which is often activated in different types of cancers. Selumetinib blocks MEK activity and inhibits growth of MEK-pathway-activated cell lines. It demonstrates anti-tumour effects in genetically engineered mouse models of neurofibroma, in which neurofibromatosis type 1 is deleted in Schwann cells.
	Important information about its composition: None.
Hyperlink to the Product Information	KOSELUGO, Product Information
Indication(s) in the EEA	**Current:** Treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above
	Proposed: Capsules Treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and older. Granules in capsules for opening (Granules) Treatment of paediatric patients aged 1 year to less than 7 years with NF1 who have symptomatic, inoperable PN.

Table 1-1 Product(s) overview

Dosage in the EEA	**Current:** 25 mg/m^2 of body surface area (BSA), taken orally BID (approximately every 12 hours). Dose is 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). The recommended dosage for patients with a BSA less than 0.55 m^2 has not been established.
	Proposed: Capsules The recommended dose of KOSELUGO is 25 mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours). Dosing in adult and paediatric patients 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). The recommended dosage for patients with a BSA less than 0.55 m^2 has not been established. Granules The recommended dose of KOSELUGO is equivalent to 25 mg/m^2 of 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).
Pharmaceutical form(s) and strengths	**Current:** Capsule formulation of the hydrogen sulfate salt (selumetinib hydrogen sulfate) presented in 10 mg and 25 mg strengths.
	Proposed: Granules KOSELUGO 5 mg granules in capsules for opening Each capsule contains 5 mg of selumetinib (as hydrogen sulfate). KOSELUGO 7.5 mg granules in capsules for opening Each capsule contains 7.5 mg of selumetinib (as hydrogen sulfate).
Is/will the product be subject to additional monitoring in the EU?	Yes

ATC, anatomical therapeutic chemical classification; ERK, extracellular signal related kinase; EEA, European Economic Area; EU, European Union; INN, international non-proprietary name; MEK, mitogen-activated protein kinase kinase; RMP, Risk Management Plan.

2. PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

2.1.1 Neurofibromatosis type 1 and plexiform neurofibromas

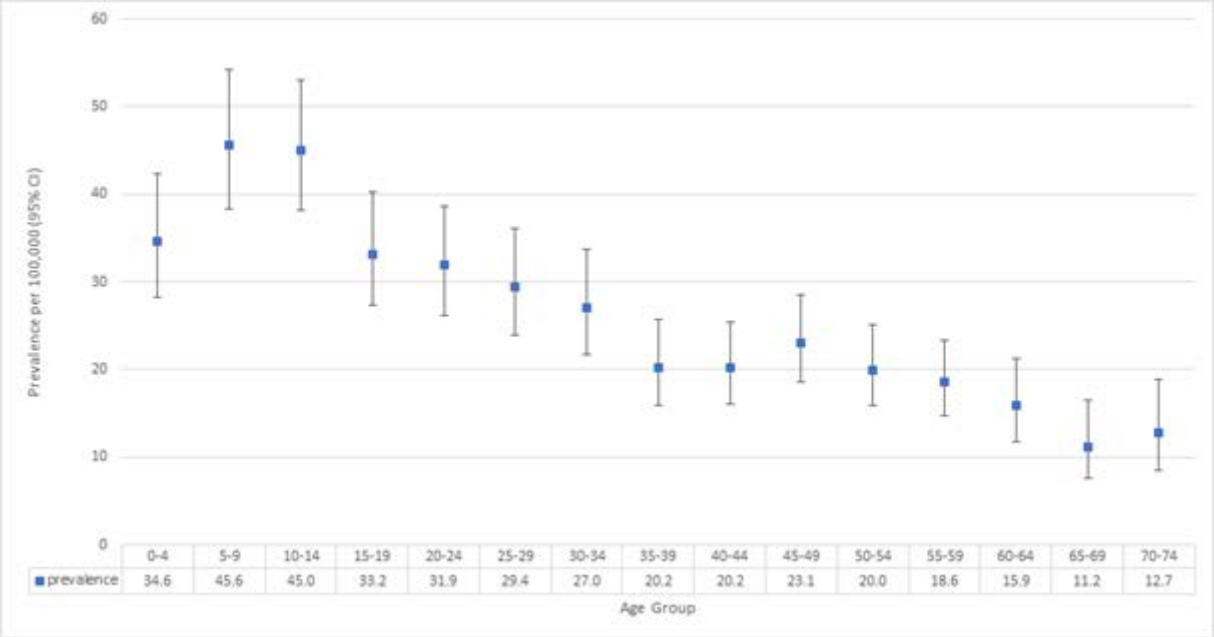
Incidence:

Neurofibromatosis type 1 (NF1) is a rare, autosomal dominant genetic disorder (inherited or de novo) caused by germline mutations in the NF1 tumour suppressor gene (17q11.2), which encodes the tumour suppressor protein neurofibromin 1. Inherited NF1 cases range from ~50% to ~70%, while de novo cases range from ~30% to ~50% (Alves et al 2019, Cimino and Gutmann 2018, Ly and Blakeley 2019, Wilson et al 2021). Most studies in Europe have consistently reported the incidence (also referred to as 'birth prevalence' in genetic disorder epidemiology) of NF1 to range from ~27 to ~37 cases per 100,000 live births (Evans et al 2010, Huson et al 1989, Lammert et al 2005, Poyhonen et al 2000), with the highest reported birth prevalence of ~53 per 100,000 live births in a population-based study from Finland (Uusitalo et al 2015); the authors attributed this more recent, relatively high birth prevalence estimate to efficient national ascertainment and increased awareness and diagnosis over time.

Prevalence:

Studies that included both adult and paediatric populations reported prevalence estimates of NF1 between ~22 to ~25 per 100,000 persons (Evans et al 2010, Huson et al 1989, Kallionpää et al 2018, Poyhonen et al 2000), whereas, studies focusing only on paediatric populations or adolescents found slightly higher prevalence estimates ranging from ~18 to ~34 per 100,000 persons (Lammert et al 2005, McKeever et al 2008, Poyhonen et al 2000). Prevalence varies by age: some cases are first diagnosed in childhood, but an even higher proportion is identified during adolescence or early adulthood. However, given the high premature mortality rates in NF1, prevalence is lower in older age groups Lammert et al 2005). Figure 1 presents prevalence estimates in each 5-year age band from 0 to 74 years (Kallionpää et al 2018).

Figure 1 - Age-specific prevalence for NF1



Based on observed prevalence in 2005.

CI, confidence interval; NF1, neurofibromatosis type 1.

Source: Kallionpää et al 2018.

Patients with NF1 have an increased risk of developing tumours of the central and peripheral nervous system including plexiform neurofibromas (PNs). PNs are histologically benign nerve sheath tumours, which typically grow along large nerves and plexi (Ferner et al 2007). Estimates of PN frequency in NF1 patients vary widely in the literature based on type of study, diagnostic criteria, and method of diagnosis (ie, magnetic resonance imaging [MRI]vs clinical exam).

Generally, PNs have been identified in between ~25% to ~50% of NF1 patients (Darrigo et al 2007, Karaconji et al 2019, Ly and Blakeley 2019, Mautner et al 2008). By MRI, PN is generally observed in 49% to 65% of adult and 11% to 36% paediatric NF1 cases (Darrigo et al 2022, Ejerskov et al 2023, Jett et al 2015, Kaas et al 2013, Kang et al 2022, Kim and Cheon 2014, Kokkinou et al 2019, Nguyen et al 2011, Nguyen et al 2012). Clinical exams typically report PN frequencies ≤ 40% of NF1 cases (Basto et al 2022, Canavese and Krajbich 2011, Cnossen et al 1998, Darrigo et al 2007, Darrigo et al 2022, Huson et al 1988, Kokkinou et al 2019, McKeever et al 2008, Noble et al 2007, Prada et al 2012, Santos et al 2020, Trevisson et al 2017). A clinical exam alone may overlook asymptomatic, benign, or internal PNs (Nguyen et al 2011). The frequency of symptomatic inoperable PN ranges from 32.5% to 52.3% for all ages, and from 35% to 50% in patients aged < 20 years (Darrigo et al 2022, Ejerskov et al 2023, Yang et al 2022).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Age

Prevalence is somewhat higher in young children than adults, a difference that results partially from early death of NF1 patients and earlier diagnoses in more recent years (Kallionpää et al 2018). Fifty percent of patients show characteristic clinical features by age 1 and 97% by age 8 (Wilson et al 2021), with an average age at onset of 4.6 years (DeBella et al 2000). NF1 can be diagnosed in 85% of patients before age 18 (Corsello et al 2018). The median age of diagnosis for de novo cases is 9.5 years versus 5 years for inherited cases (Evans et al 2010).

Gender

NF1 affects men and women equally (Alves et al 2019, Corsello et al 2018, Karaconji et al 2019, Ly and Blakeley 2019, Mansouri et al 2017, Williams et al 2009, Yamauchi et al 2019). In Finland, prevalence in children is significantly lower among girls than boys. However, sex differences are attributed to delayed diagnosis of girls rather than a sex difference in incidence (median age at diagnosis among men is 9.9 years vs 17.9 years among women) (Kallionpää et al 2018).

Racial/ethnic origin

While NF1 is independent of race and ethnicity, differences may exist for penetrance and expressivity, such as paediatric brain tumours (Abadin et al 2015, Wilson et al 2021). Limited population-based studies outside of Europe make it unclear if there are differences across geographies.

Risk factors

As NF1 is an autosomal dominant genetic disorder, the most obvious risk factor for disease is a mutation (inherited or de novo) in the NF1 gene. Increased paternal age has been identified as a potential risk factor, but studies have shown inconsistent results confirming this (Huson et al 1989).

The cause of de novo NF1 mutations is unknown, but the unusually high frequency of them (accounting for 30% to 50% of NF1 cases) may be related to the large size of the gene, which has 2,818 amino acids (Alves et al 2019, Cimino and Gutmann 2018).

The only established risk factor for symptom onset is age: symptoms increase with age (Karaconji et al 2019, Ly and Blakeley 2019, Wilson et al 2021). Disease expression is highly variable, even within the same family, and the onset of symptoms in terms of timing, types,

and severity generally cannot be predicted by the specific NF1 mutation (Alves et al 2019, Karaconji et al 2019, Wilson et al 2021).

The main existing treatment options:

To date, there is no efficacious medical treatment that has been shown to prevent, cure, or durably reverse the growth of NF1-related PNs.

Currently, the only available options to treat and manage NF1-related PN are pain management, surgical excision to remove as much of the PN as possible, and therapy with selumetinib for the treatment of symptomatic, inoperable PNs in paediatric patients with NF1 aged 3 years and above. 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). 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). Additionally, tumour regrowth often occurs (17% to 44% after initial resection), further contributing to the cautious approach taken for the surgical management of NF1 patients with PNs (Needle et al 1997, Nguyen et al 2013, Safaee et al 2015). Hence, surgery is not deemed appropriate for all patients.

Several targeted biological therapies to treat PNs are currently being investigated in clinical trials, including selumetinib, mirdametinib, sirolimus, tipifarnib, imatinib mesylate and sorafenib. The development of mitogen-activated protein kinase kinase (MEK) inhibitors, which target a key component in the RAS signalling pathway, has significantly transformed the management of PN. Clinical trials, specifically Phase 1/2 studies of the MEK inhibitor selumetinib in children with inoperable and symptomatic PN, demonstrated clinically significant overall response rate and durable response in children. Consequently, selumetinib received the United States Food and Drug Administration approval as the first medical therapy for managing PN in paediatric patients (Fisher et al 2022). Currently, there are no existing clinical guidelines and medical treatment for adult patients with NF1-PN.

Natural history of the indicated condition in the (untreated) population, including mortality and morbidity:

NF1 affects multiple organ systems and is characterised by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations very early in life. The condition progresses gradually over an individual's lifetime; however, there is wide variety in the type of manifestations. Neurofibromas, including PNs, are the most common benign tumours in patients with NF1.

PNs may appear as focal growths or extend longitudinally along a nerve and involve multiple fascicles. Generally, PNs have a complex shape and slow overall growth rate. NF1-related

PNs typically appear at birth but may continue to appear through late adolescence and early adulthood (Williams et al 2009). Rapid growth of PNs is most prominent during early infancy, as well as in adolescence and during pregnancy (Rosser and Packer 2002). A weak correlation between male sex and NF1-related PNs was observed in a 2012 study (Nguyen et al 2012). PNs are associated with a variety of debilitating comorbidities that impact children from early childhood (usually before 5 years of age) through their entire lifespan. Although PNs may develop from nerves anywhere in the body, they are frequently located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck-brachial plexus, and/or lumbosacral plexus. Volumes can reach up to 20% of body weight (Dombi et al 2007, Korf 1999, Mautner et al 2008). A longitudinal study using electronic medical records from Danish NF1 centres found that large PN (≥ 3 cm) most frequently occurred in paediatric patients in the trunk (30%), legs (23%), head/neck (18%), and arms (18%), while large PN in adult occurred in the legs (29%), trunk (26%), and head/neck (25%) (Ejerskov et al 2023).

PNs can result in severe pain, neurological impairment, motor dysfunction, respiratory compromise and disfigurement. Acute and/or chronic PN-related pain are common symptoms and have a considerable effect on quality of life. The visible complications of NF1 also affect emotional quality of life in children and adolescents (Gutmann et al 2017). Kim et al 2009 described that among 47 children and young adults with NF1-related PN enrolled in clinical studies conducted by the National Cancer Institute Paediatric Oncology Branch, 53% had undergone surgery prior to trial entry, 60% had disfigurement, 34% required pain medication, 19% had neurologic symptoms, 11% had airway compromise, and 4% died as a result of PN progression.

NF1 is associated with an overall decrease in life expectancy of 8 to 15 years compared to the general population, based on findings from cohort studies of NF1 patients in the UK, Sweden, and Denmark (Evans et al 2011, Sorensen et al 1986, Zöller et al 1995). In a Finnish population-based study using hospital records, which covers all specialties and secondary and tertiary centres to identify NF1 patients, women with NF1 had a lower life expectancy than men with NF1 (life span shortened 26.1 years vs 16.5 for men) and a higher standardised mortality ratio (4.02 [95% confidence interval [CI]: 3.32-4.83] vs 2.66 [95% CI: 2.19-3.22], respectively) (Uusitalo et al 2015).

PN can result in life-threatening morbidities such as compression of the trachea or great vessels. There is a 8% to 16% lifetime risk of PN transformation into malignant peripheral nerve sheath tumours, which are the leading cause of poor survival in NF1 patients. (Evans et al 2011, Karaconji et al 2019, Ly and Blakeley 2019, Nguyen et al 2011, Prada et al 2012, Wilson et al 2021). Risk estimates of 5-year survival in NF1 patients who develop malignant peripheral nerve sheath tumours are described variously in the literature as 15% to 50% (Ly and Blakeley 2019) or up to 60% (Karaconji et al 2019).

Aside from neurofibromas, other NF1 manifestations include skeletal abnormalities (eg, scoliosis, osteopenia, orbital dysplasia, tibial dysplasia and pseudoarthrosis), low grade gliomas and an increased risk of some malignant tumours (see section on important co-morbidities) (Gutmann et al 2017).

Important co-morbidities:

Leukaemia (especially juvenile chronic myelogenous leukaemia) and myelodysplastic syndromes are infrequent but more common among children with NF1 vs. those without. Other tumours seen more often than expected in individuals with NF1 include rhabdomyosarcomas, pheochromocytomas, gastrointestinal (GI) stromal tumours, glomus tumours, and retinal vasoproliferative tumours (Friedman 2018), brain tumours, endocrine cancers, connective tissue malignancies, and breast cancer (Uusitalo et al 2015, Walker et al 2006).

There is a high incidence (at least 10% of patients; Lammert et al 2006) of skeletal abnormalities in patients with NF1, including reduced bone mineral density, increased fracture rates, scoliosis, long bone dysplasia and pseudoarthrosis, and sphenoid wing dysplasia, which may be expected to have an effect on underlying bone metabolism and calcium and phosphate levels. Children with NF1 have significantly lower vitamin D concentrations than controls, which may impact bone homeostasis (Stevenson et al 2011).

Major cardiac abnormalities, particularly congenital heart defects and hypertrophic cardiomyopathy, are more frequent in patients with NF1 whole-gene deletions compared to NF1 patients without such deletions (Nguyen et al 2013). Valvular pulmonic stenosis is also more common in individuals with NF1 compared to the general population (Lin et al 2000). Hypertension is frequently seen among patients with NF1 with a prevalence of around 16% (Lama et al 2004) in most cases the hypertension is essential and may develop at any age (Friedman 2018). Those diagnosed with NF1 also have a 4-fold increased risk of mortality from respiratory diseases (Uusitalo et al 2015).

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Gastrointestinal effects

Administration of selumetinib in mice, rats and monkeys resulted in GI tract changes. Daily oral dosing of selumetinib in rats was associated with soft faeces at free exposures (area under the plasma concentration-time curve [AUC]) ≥ 2.6-fold the free clinical exposure at the maximum human recommended dose (MHRD) of 25 mg/m^2 twice daily (BID). In monkeys, persistent diarrhoea associated with secondary changes (dehydration, serum chemistry abnormalities and renal tubular microscopic changes) was observed following daily administration of selumetinib at exposures (AUC) similar to the clinical exposure at MHRD. In mice, selumetinib administration resulted in ulcerative and inflammatory GI findings at exposures similar to the clinical exposure at MHRD. At systemic exposures (free AUC) 28-fold greater than the free clinical exposure, the GI findings in mice were associated with inflammatory cell infiltration of the portal area in the liver with no changes in plasma biomarkers and bone marrow hypo cellularity with decreases in circulating red blood cell parameters and reactive hyperplasia in lymph nodes. The GI changes and associated secondary findings in rodents and monkeys showed partial or full reversibility following a recovery period.

The GI disturbances observed in the non-clinical studies, appear to be clinically relevant as diarrhoea, nausea and vomiting have been reported in patients treated with selumetinib. However, these effects are not considered important safety concerns as they can be adequately managed through routine measures and diarrhoea, nausea, stomatitis and dry mouth are included in Section 4.8 of the Summary of Product Characteristics (SmPC).

Skin effects

Daily administration of selumetinib in rats was associated with ulcerative and inflammatory skin changes that correlated with clinical findings of skin lesions and scabs. Skin findings were observed at free systemic exposures (AUC) similar or greater than the free clinical exposure at MHRD. The skin findings are expected to be reversible following a recovery period.

Skin findings observed in the non-clinical studies appear to be relevant as skin rashes have been reported in patients treated with selumetinib. However, these findings do not raise any important safety concerns for human use. Skin and subcutaneous tissue disorders such as rash (including rash acneiform), dry skin, paronychia and hair changes are included in Section 4.8 of the SmPC.

Physeal dysplasia

In a 3-month study in rats, selumetinib administration resulted in microscopic findings in the femoro-tibial joint (physeal dysplasia; decreased cellularity in the bone marrow femur adjacent to the physis). Physeal dysplasia was observed in rats at exposure multiples that exceeded the free systemic clinical exposure (AUC) at MHRD by approximately 11-fold (60 times the total clinical exposure). Physeal dysplasia was not observed in mice or monkeys following oral administration of selumetinib for up to 6-months.

No changes in the bone growth or signs of physeal dysplasia have been detected in paediatric patients treated with selumetinib. However, it is unknown whether long-term use of selumetinib could have an effect on bone growth in these patients. Therefore, based on non-clinical findings, physeal dysplasia is considered a safety concern for paediatric use.

Soft tissue mineralisation

Dosing of selumetinib resulted in soft tissue mineralisation in a variety of tissues (gastric mucosa, cornea, kidney, liver, myocardium, skeletal muscle and stomach) in rodents. In rats, mineralisation was associated with changes in plasma inorganic phosphate, albumin and/or calcium. Soft tissue mineralisation in rats and mice were observed at exposure multiples that were 2.6- and 19.5-fold higher than the clinical exposure at MHRD, respectively. The soft tissue mineralisation remained unchanged following a recovery period.

Soft tissue mineralisation has not been seen in monkeys treated with selumetinib or in dogs treated with other MEK inhibitors at exposures significantly higher than those in rats. This suggests that rodents may be more sensitive to the development of this toxicity than non-rodents. These findings do not raise any important safety concerns for human use.

Urinary lower tract obstruction

In a 26-week mouse study, selumetinib was associated with vascular engorgement of the corpus cavernosum of the bulbocavernosus muscle in male mice following dosing for > 8 to 15 weeks (at a free exposure 28 times the clinical free exposure at the MHRD). In some animals, this resulted in obstruction of the urinary tract and back flow pressure effects leading to premature death. These findings were specific to male mice and were not seen in any other of the rodent toxicity studies or following dosing of cynomolgus monkeys for up to 26 weeks.

The non-clinical findings were observed at significant multiples of the clinical exposure only in male mice, in addition there is no evidence from studies that these findings translate into clinical findings, thus this observation does not raise any important safety concerns for human use.

Reproductive/developmental toxicity

Fertility

In a 6-month mouse study, selumetinib did not affect male mating performance at free exposures approximately 22 times the human clinical exposure at the MHRD. In female mice exposed to selumetinib, mating performance and fertility were not affected. The free exposure (AUC) at the no observed adverse effect level for maternal toxicity and effects on reproductive performance was approximately, 3.5-fold the free clinical exposure at the MHRD. Although mating performance and fertility were not affected the number of live foetuses was slightly reduced in the female fertility study at a free exposure 22-fold the clinical exposure at the MHRD. Following a 3-week treatment withdrawal period, no effects were apparent on any parameter.

Embryo foetal toxicity

In embryo foetal development studies in mice, selumetinib caused a reduction in the number of live foetuses due to an increase in post-implantation loss, a reduction in mean foetal and litter weights, increased occurrence of open eye and cleft palate at dose levels that did not induce significant maternal toxicity. These effects were seen at a free exposure (AUC) 3.5-fold the free clinical exposure at MHRD and indicated that selumetinib may have potential to cause defects on the foetus.

Pre- and postnatal development

Administration of selumetinib to pregnant mice from gestation Day 6 through to lactation Day 20 resulted in reduced pup body weights, and fewer pups met the pupil constriction criterion on Day 21 post-partum. Malformations occurred at a maternal free plasma

concentration (maximum plasma concentration [C_{max}]) 0.4-fold below the mean free clinical concentration at MHRD.

Selumetinib and its active metabolite were excreted in the milk of lactating mice at concentrations approximately the same as those in plasma.

The reproductive and developmental toxicity data indicate that selumetinib may cause foetal harm in female patients of child bearing potential.

Genotoxicity

Selumetinib showed no mutagenic or clastogenic potential in vitro but produced an increase in micronucleated immature erythrocytes (chromosome aberrations) in mouse micronucleus studies, predominantly via an aneugenic mode of action. The free mean exposure (C_{max}) at the no observed effect level was approximately 27-times greater than clinical free exposure at the MHRD.

Carcinogenicity

Selumetinib was not carcinogenic in a 6-month study in rasH2 transgenic mice at free exposures 24 times (females) and 16 times (males) the clinical free AUC at MHRD and in a 2-year carcinogenicity study in rats at free exposures 2.9 times (females) and 3.7 times (males) the clinical free AUC at MHRD.

2.2.2 Safety pharmacology

Cardiovascular system, including potential effect on the QT interval

Selumetinib and N-desmethyl selumetinib did not inhibit the human ether-à-go-go-related gene current at maximum test concentrations which were both at least 390-fold greater than the free plasma C_{max} of selumetinib (11.69 ng/mL ≡ 0.026 μM) and N-desmethyl selumetinib (1.13 ng/mL ≡ 0.003 μM) at the MHRD.

Oral administration of selumetinib to conscious, unrestrained minipigs had no effects on arterial blood pressures (mean, systolic and diastolic), heart rate, or electrocardiogram parameters, including on corrected QT interval, at a free C_{max} approximately 2-fold the clinical free C_{max} at MHRD. There were no apparent treatment related effects on the electrocardiogram in the cynomolgus monkey repeat dose toxicity studies.

Nervous system

Single oral doses of selumetinib produced no adverse effects on body temperature or on neurological or behavioural indices in rats for up to 24 hours post-dose.

Respiratory system

Single oral administration of selumetinib produced no effects on tidal volume, respiratory rate, lung dynamic compliance or minute volume in anaesthetised rats.

2.2.3 Other toxicity-related information or data

Phototoxicity

Selumetinib did not demonstrate a risk for phototoxicity at free C_{max} > 8,000 × the clinical free C_{max} achieved at MHRD.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

2.3.1 NF1-PN adult population (KOMET)

The primary support for the safety of selumetinib in adult patients with NF1-PN derives from the pivotal Phase III study KOMET (D134BC00001) in 145 adult patients with inoperable and symptomatic NF1-PN with the data cut-off date of 05 August 2024.

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

The demographic characteristics of all randomised patients are provided in Table 2-1. The duration of exposure in the selumetinib-treated patients in on-selumetinib period is provided in Table 2-2.

Table 2-1 Age group, sex, and race of randomised patients (KOMET)

Variable	Selumetinib (N = 71)	Placebo (N = 74)	Total (N = 145)[b]
Age (years) [a]			
Mean	32.6	29.8	31.2
SD	11.42	8.72	10.19
Min	18	18	18
Median	31	28	29
Max	60	53	60
Sex, n (%)			
Female	38 (53.5)	32 (43.2)	70 (48.3)
Male	33 (46.5)	42 (56.8)	75 (51.7)
Race, n (%)			
Asian	22 (31)	23 (31.1)	45 (31.0)
Black or African American	6 (8.5)	3 (4.1)	9 (6.2)
White	38 (53.5)	43 (58.1)	81 (55.9)
Other	2 (2.8)	3 (4.1)	5 (3.4)
Not reported	3 (4.2)	2 (2.7)	5 (3.4)

KOMET data cut-off date 05 August 2024.

Max, maximum; min, minimum; SD, standard deviation.

[a] Age at screening.

[b] Total (N = 145) includes all patients in the study even those that did not receive selumetinib; the total number of patients that received selumetinib is N = 137.

Table 2-2 Duration of exposure – on-selumetinib period (KOMET)

Variable	Selumetinib (N = 71)	Placebo/selumetinib (N = 66)	Total (N = 137)
Total exposure (days) [a]			
Mean	523.5	276.2	404.4
SD	223.91	145.92	226.63
Min	11	10	10
Median	554.0	267.0	364.0
Max	958	620	958
Total treatment days	37,170	18,232	55,402

KOMET data cut-off date 05 August 2024.

Max, maximum; min, minimum; SD, standard deviation.

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

2.3.2 Selumetinib granular formulation (SPRINKLE)

The use of the granule form of KOSELUGO in paediatric patients with symptomatic inoperable NF1-related PN is supported by the data from the pivotal Phase I/II study SPRINKLE (D1346C00004), conducted in children ≥ 1 to < 7 years of age with NF1-related PN, with the data cut-off date of 08 April 2024.

Data from the SPRINKLE study are not included in the overall paediatric pool at this time since the duration of exposure in SPRINKLE at the data cut-off date (08 April 2024) was short (at least 3 cycles) compared with the studies in the NF1-PN paediatric capsule pool (refer to Section 2.3.3).

The median duration of exposure to selumetinib in the SPRINKLE study was 329.5 days overall (range: 83 to 771 days) and the median actual duration (total exposure minus total duration of dose interruptions) was 313.3 days (range 83 to 771 days). The demographic characteristics of the exposed population are provided in Table 2-3.

Table 2-3 Age group, sex, and race (SPRINKLE)

Variable	SPRINKLE (N = 36)
Age group, n (%)	

Table 2-3 Age group, sex, and race (SPRINKLE)

Variable	SPRINKLE (N = 36)
< 2 years	7 (19.4)
2 to ≤ 3 years	11 (30.6)
> 3 [a]	18 (50.0)
Sex, n (%)	
Female	14 (38.9)
Male	22 (61.1)
Race, n (%)	
Asian	5 (13.9)
Black or African American	1 (2.8)
White	22 (61.1)
Other	4 (11.1)
Not reported	4 (11.1)

SPRINKLE data cut-off date 08 April 2024.

[a] SPRINKLE was conducted in children ≥ 1 to ≤ 7 years of age (at time of enrolment).

2.3.3 Paediatric and adult capsule pool

NF1-PN

The NF1-PN paediatric capsule pool (N = 126) includes the safety data across the pivotal SPRINT Phase II Stratum 1 study, SPRINT Phase I study, and studies D1346C00011 (Study 11, paediatric cohort), D1346C00013 (Study 13), and D1346C00015 (Study 15) in paediatric patients with NF1-related PN. The pivotal data supporting the initial submission are from SPRINT Phase II Stratum 1, which enrolled 50 paediatric patients with NF1 who have inoperable PN with PN that had related morbidity at enrolment who received selumetinib monotherapy treatment at 25 mg/m^2 BID (dosing of selumetinib was based on body surface area [BSA]).The NF1-PN adult capsule pool (N = 153) includes the safety data from the pivotal KOMET study and study D1346C00011 (Study 11, adult cohort).

Other indications

Supportive data are provided by an adult monotherapy pool composed of 347 patients with cancer who received either selumetinib monotherapy 75 mg BID (Hyd-sulfate formulation) or 100 mg BID (free-base formulation) from 7 AstraZeneca-sponsored completed oncology studies.

The overall patient exposure to selumetinib capsule is provided in Table 2-4 by safety pools. The exposure by duration of exposure is provided in Table 2-5, while the exposure by dose is provided in Table 2-6. The demographic characteristics of patients by safety pools is provided in Table 2-7 by age group and sex and in Table 2-8 by race.

Table 2-4 Overall patient exposure to selumetinib capsule by safety pool

Studies	NF1-PN paediatric capsule pool (N = 126)	NF1-PN adult capsule pool (N = 153)	Adult monotherapy pool (N = 347)
Paediatric studies			
SPRINT Phase II, Stratum 1* 25 mg/m^2 BID	50	-	-
SPRINT Phase I* 20 mg/m^2, 25 mg/m^2 or 30 mg/m^2 BID	24	-	-
D1346C00011 (Study 11) 25 mg/m^2 BID	16	-	-
D1346C00013 (Study 13) 25 mg/m^2 BID	12	-	-
D1346C00015 (Study 15) 25 mg/m^2 BID	24	-	-
Adult studies			
KOMET 25 mg/m^2 BID	-	137	-
D1346C00011 (Study 11) 25 mg/m^2 BID	-	16	-
Selumetinib Hyd-sulfate 75 mg BID – 3 studies	-	-	79
Selumetinib free-base 100 mg BID – 4 studies	-	-	268

NF1-PN paediatric capsule pool: SPRINT Phase I (data cut-off date 27 February 2021), SPRINT Phase II Stratum 1 (data cut-off date 31 March 2021), D1346C00011 (data cut-off date 15 August 2023), D1346C00013 (data cut-off date 23 December 2022), and D1346C00015 (data cut-off date 24 April 2023).

NF1-PN adult capsule pool: KOMET (data cut-off date 05 August 2024); D1346C00011 (data cut-off date 15 August 2023).

BID, twice daily; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

* Externally sponsored study

Table 2-5 Duration of exposure

Duration of exposure	Number of patients	Person time (years)
NF1-PN paediatric capsule pool		
< 12 months	8	4.3
≥ 12 to ≤ 24 months	46	69.8
> 24 to ≤ 36 months	22	51.9
> 36 months	50	268.4
Total	126	394.4
NF1-PN adult capsule pool		
< 12 months	71	41.8
≥ 12 to ≤ 24 months	64	99.2
> 24 to ≤ 36 months	18	42.4
> 36 months	0	0
Total	153	183.4
Adult monotherapy pool		
< 6 months	306	55.3
6 to < 12 months	31	20.4
12 to < 18 months	10	11.4
Total	347	87.1

NF1-PN paediatric capsule pool: SPRINT Phase I (data cut-off date 27 February 2021), SPRINT Phase II Stratum 1 (data cut-off date 31 March 2021), D1346C00011 (data cut-off date 15 August 2023), D1346C00013 (data cut-off date 23 December 2022), and D1346C00015 (data cut-off date 24 April 2023).

NF1-PN adult capsule pool: KOMET (data cut-off date 05 August 2024); D1346C00011 (data cut-off date 15 August 2023).

NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

Table 2-6 Exposure by dose of selumetinib

Dose	Number of patients	Person time (years)
NF1-PN paediatric capsule pool		
Selumetinib Hyd-sulfate 20 mg/m^2 BID	12	60.5
Selumetinib Hyd-sulfate 25 mg/m^2 BID	108	308.3
Selumetinib Hyd-sulfate 30 mg/m^2 BID	6	25.6
Total	126	394.4
NF1-PN adult capsule pool		
Selumetinib Hyd-sulfate 25 mg/m^2 BID	153	183.4
Total	153	183.4

Table 2-6 Exposure by dose of selumetinib

Dose	Number of patients	Person time (years)
Adult monotherapy pool		
Selumetinib Hyd-sulfate 75 mg BID	79	16.3
Selumetinib free-base 100 mg BID	268	70.8
Total	347	87.1

NF1-PN paediatric capsule pool: SPRINT Phase I (data cut-off date 27 February 2021), SPRINT Phase II Stratum 1 (data cut-off date 31 March 2021), D1346C00011 (data cut-off date 15 August 2023), D1346C00013 (data cut-off date 23 December 2022), and D1346C00015 (data cut-off date 24 April 2023).

NF1-PN adult capsule pool: KOMET (data cut-off date 05 August 2024); D1346C00011 (data cut-off date 15 August 2023).

BID, twice daily; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

Table 2-7 Exposure by age group and gender

Age group*	Number of patients		Person time (years)	
	Male	Female	Male	Female
NF1-PN paediatric capsule pool				
< 12 years	31	27	121.5	98.8
≥ 12 to 18 years	36	32	100.9	73.2
Total	67	59	222.4	172.0
NF1-PN adult capsule pool				
18 to < 30 years	42	40	49.4	48.4
30 to < 65 years	37	34	46.4	39.3
≥ 65 years	0	0	0	0
Total	79	74	95.8	87.6
Adult monotherapy pool				
19 to < 35 years	6	10	1.1	2.5
35 to < 50 years	30	33	7.5	9.6
50 to ≤ 65 years	113	55	25.5	13.3
> 65 years	58	42	16.4	11.2
Total	207	140	50.5	36.6

NF1-PN paediatric capsule pool: SPRINT Phase I (data cut-off date 27 February 2021), SPRINT Phase II Stratum 1 (data cut-off date 31 March 2021), D1346C00011 (data cut-off date 15 August 2023), D1346C00013 (data cut-off date 23 December 2022), and D1346C00015 (data cut-off date 24 April 2023).

NF1-PN adult capsule pool: KOMET (data cut-off date 05 August 2024); D1346C00011 (data cut-off date 15 August 2023).

NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

* Age at time of enrolment.

Table 2-8 Exposure by race

Race	Number of patients	Person time (years)
NF1-PN paediatric capsule pool		
White	83	294.0
Black or African American	6	15.7
Asian	32	70.5
Other	5	14.1
Total	126	394.4
NF1-PN adult capsule pool		
White	74	83.5
Black or African American	9	11.2
Asian	60	79.0
Other	10	9.7
Total	153	183.4
Adult monotherapy pool		
White	327	83.8
Black or African American	6	0.7
Asian	7	1.4
Other	4	0.6
Not reported	3	0.7
Total	347	87.1

NF1-PN paediatric capsule pool: SPRINT Phase I (data cut-off date 27 February 2021), SPRINT Phase II Stratum 1 (data cut-off date 31 March 2021), D1346C00011 (data cut-off date 15 August 2023), D1346C00013 (data cut-off date 23 December 2022), and D1346C00015 (data cut-off date 24 April 2023).

NF1-PN adult capsule pool: KOMET (data cut-off date 05 August 2024); D1346C00011 (data cut-off date 15 August 2023).

NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

2.4 MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Patients less than 3 years of age

Reason for exclusion: Selumetinib capsule cannot be crushed or broken. Patients under 3 years of age were considered as not capable of swallowing the whole capsule and were excluded. The youngest patient enrolled in SPRINT Phase II study was 3.5 years of age.

Is it considered to be included as missing information: No

Rationale: Selumetinib was not initially indicated for use in patients less than 3 years, with NF1 and symptomatic, inoperable PN. Therefore, this population was not relevant for consideration as missing information. A granule formulation has since been made available, allowing patients ≥1 years to receive selumetinib.

Pregnant or breast feeding female patients

Reason for exclusion: Pregnant or breast feeding female patients were excluded due to potential risk of foetal and teratogenic adverse events (AEs) of an investigational agent.

Is it considered to be included as missing information: No

Rationale: A warning is included in Section 4.4 of the SmPC to state that selumetinib is not recommended in women of child bearing potential who are not using contraception. Section 4.6 (Pregnancy, lactation and fertility) of the SmPC recommends female patients of child bearing potential to avoid becoming pregnant and to use effective contraception. Moreover, selumetinib is indicated in a young population, only a small proportion would be of child bearing potential and there is a low likelihood of unplanned pregnancy due to the warnings in Section 4.4. Therefore, exposure in this population is expected to be very limited and this population is not relevant for consideration as missing information.

Prior treatment with selumetinib or other specific MEK1/2 inhibitor (unless the patient meets criteria for re-treatment). Ongoing radiation therapy, chemotherapy, hormonal therapy directed at the tumour, immunotherapy, or biologic therapy. Use of an investigational agent within the past 30 days (of note, patients in the pivotal SPRINKLE study were allowed to have received prior treatment with MEK1/2 inhibitors).

Reason for exclusion: To avoid factors that may confound understanding of the safety profile and efficacy of selumetinib, and to ensure appropriate interpretation of the safety data.

Is it considered to be included as missing information: No

Rationale: There is no evidence to suggest that the safety profile of selumetinib in this population would differ from that of the target population. This population is therefore not relevant for consideration as missing information.

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.

Reason for exclusion: To allow patients to tolerate selumetinib treatment, and to ensure the optimal assessment of the efficacy and safety profile of selumetinib.

Is it considered to be included as missing information: No

Rationale: Selumetinib is contraindicated in patients with severe hepatic disease (Section 4.3 of the SmPC). For the remaining exclusions, there is no evidence to suggest that the safety profile in this patient population is different to that of the general target population. This population is therefore not relevant for consideration as missing information.

Refractory nausea and vomiting, chronic gastrointestinal diseases (eg, inflammatory bowel disease), or significant bowel resection that would preclude adequate absorption.

Reason for exclusion: To exclude patients who may have inadequate absorption, so that patients receive optimal dose of selumetinib treatment for assessment of the efficacy profile of selumetinib.

Is it considered to be included as missing information: No

Rationale: There is no scientific rationale to suspect that the safety profile for this patient population could differ to that of the target population. Therefore, use of selumetinib in this population is not considered to be an area of missing information.

Ophthalmologic conditions, such as:

- **current or past history of central serous retinopathy.**
- **current or past history of retinal vein occlusion (RVO).**
- **known intraocular pressure (IOP) > 21 mmHg (or upper limit of normal adjusted by age) or uncontrolled glaucoma (irrespective of IOP).**
- **patients with known glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) and are not experiencing pain related to the glaucoma, may be eligible after discussion with the study chair.**
- **subjects with any other significant abnormality on ophthalmic examination should 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 longstanding orbito temporal PN (such as visual loss, strabismus).**

Reason for exclusion: The class of MEK inhibitors, which includes selumetinib, are known to have an effect on vision.

Is it considered to be included as missing information: No

Rationale: The excluded populations may have a different safety profile to that of the general target population as they may be at an increased risk of ocular events. Section 4.2 provides dose modification advice for ocular toxicities, Section 4.4 provides Warnings and Precautions with regards to ocular toxicities, and Section 4.8 includes blurred vision as an adverse drug reaction (ADR). In addition, ocular toxicity is included as an important potential risk for selumetinib. Therefore, use of selumetinib in this population is not considered to be an area of missing information.

Patients not achieving adequate blood pressure in spite of antihypertensive therapy for control of blood pressure.

Reason for exclusion: To allow optimal assessment of the safety profile of selumetinib in the target patient population.

Is it considered to be included as missing information: No

Rationale: The excluded population may be at an increased risk of cardiovascular events if adequate blood pressure is not achieved in spite of antihypertensive therapy. However, Section 4.8 of the SmPC includes increased blood pressure as an ADR for which there is a step wise dose reduction based on the Common Terminology Criteria for Adverse Events (CTCAE) grade of the event. This population is therefore not relevant for consideration as missing information.

Supplementation with vitamin E greater than 100% of the daily recommended dose.

Reason for exclusion: Selumetinib capsules contain D-α-tocopheryl polyethylene glycol succinate, which may be a source of vitamin E. High doses of vitamin E may increase the risk of bleeding in patients taking concomitant anticoagulant or antiplatelet medications (eg, warfarin or aspirin).

Is it considered to be included as missing information: No

Rationale: Vitamin E is not an essential medication and Section 4.4 of the SmPC contains a warning that vitamin E supplementation should be avoided with the capsule formulation. The

risk of coadministration with vitamin E is therefore considered unlikely and as such is not considered relevant as missing information.

Cardiac function, such as:

- **known inherited coronary disease**
- **symptomatic heart failure (New York Heart Association [NYHA] Class II-IV prior or current cardiomyopathy, or severe valvular heart disease)**
- **prior or current cardiomyopathy**
- **severe valvular heart disease**
- **history of atrial fibrillation.**

Reason for exclusion: The class of MEK inhibitors, which includes selumetinib, are known to have an effect on cardiac function.

Is it considered to be included as missing information: No

Rationale: The excluded population may be at an increased risk of cardiovascular events resulting from decreased cardiac function, such as left ventricular ejection fraction (LVEF) reduction. However, Section 4.4 of the SmPC describes the requirement for an echocardiogram before starting treatment to establish baseline left ventricular (LV) function and a warning relating to this risk and Section 4.8 includes ejection fraction decreased as an ADR for which there is a step wise dose reduction based on the CTCAE grade of the event included in Section 4.2 of the SmPC. In addition, left ventricular ejection fraction reduction is an important identified risk. This population is therefore not relevant for consideration as missing information.

Known severe hypersensitivity to selumetinib or any excipient of selumetinib or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib.

Reason for exclusion: To avoid potential hypersensitivity reactions (such as severe and life-threatening reactions), which could result in selumetinib treatment discontinuation, and to allow patients to derive benefit of selumetinib treatment.

Is it considered to be included as missing information: No

Rationale: There is no evidence from the selumetinib clinical development programme of a different safety profile to that of the general target population. Moreover, it is not feasible to characterise this population as the events are idiosyncratic. Therefore, use of selumetinib in this patient population is not considered to be an area of missing information.

Prior treatment with any of the following:

- **specific anti-cancer agents or systemic PN target therapies within various timeframes of starting selumetinib treatment.**
- **major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment.**
- **radiotherapy within specific timeframes, dependent on the location and field.**
- **any unresolved chronic toxicity with CTCAE Grade ≥ 2 from previous anti-NF1 therapy, except for alopecia.**

Reason for exclusion: To avoid toxicities resulting from prior treatment preventing optimal assessment of the efficacy and safety profile of selumetinib.

Is it considered to be included as missing information: No

Rationale: There is no evidence to suggest that these populations have a different safety profile to that of the target patient population. Therefore, use of selumetinib in these populations is not considered to be an area of missing information.

Evidence of an optic glioma, malignant glioma, malignant peripheral nerve sheath tumour, or other cancer requiring treatment with chemotherapy or radiation therapy.

Reason for exclusion: These populations often exhibit progressive neurologic dysfunction and are excluded to allow optimal assessment of the efficacy and safety profile of selumetinib.

Is it considered to be included as missing information: No

Rationale: There is no evidence to suggest that these populations have a different safety profile to that of the target patient population. Therefore, use of selumetinib in these populations is not considered to be an area of missing information.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged exposure.

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 2-9 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme.
Breast-feeding women	
Patient with relevant comorbidities:	
• Patients with hepatic impairment (classification of hepatic impairment using the Child-Pugh classification system)	Child-Pugh class A, B and C (n = 8 patients in each class)
• Patients with renal impairment (classification of renal impairment using the Cockcroft-Gault method)	End-stage renal disease (n = 12 patients).
• Patients with cardiovascular impairment (eg, symptomatic heart failure New York Heart Association Class II-IV, prior or current cardiomyopathy, or severe valvular heart disease) • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme
Patients with relevant different ethnic origin	NF1-PN paediatric capsule pool: White = 83; Black or African American = 6; Asian = 32; Other = 5; Total = 126 (refer to Table 2-8). NF1-PN adult capsule pool: White = 74; Black or African American = 9; Asian = 60; Other = 10; Total = 153 (refer to Table 2-8).
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme.

NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; NYHA, New York Heart Association.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Post-authorisation exposure

2.5.1.1 Method used to calculate exposure

The post-marketing patient exposure data presented is estimated based on KOSELUGO's monthly actual ex-factory sales volume from each local marketing company. These data represent KOSELUGO's only approved formulation in capsules delivered to various distribution channels (for example wholesalers, pharmacies etc) worldwide.

The sales volume is provided as the total number of capsules sold (either as 10 mg or 25 mg). KOSELUGO is available in a 10 mg or 25 mg capsule form and is taken orally twice daily (approximately every 12 hours). The dosing is individualised based on BSA in kg/m^2. Different strengths of KOSELUGO capsules are combined to attain the desired daily dose. Depending on the BSA of the patients, the recommended daily dosage could vary by a minimum of 30 mg (for patients with BSA of 0.55 to $0.69/m^2$) to a maximum of 100 mg (for patients with a BSA of $\geq 1.90/m^2$).

The current methodology does not distinguish between sales that are related to initial prescriptions versus those related to repeat prescriptions. Therefore, it is not possible to estimate the number of patients exposed to KOSELUGO capsules. More detailed patient-level data (eg, sex, race, age group, off-label use, specific populations etc) are not available.

In view of the above variations in the daily dosages and the capsule strengths of KOSELUGO administered to different patients with varying BSAs, the post-marketing patient exposure data was estimated based on the total strength of KOSELUGO sold in mg (for both 10-mg and 25-mg capsule strengths), by using the following formulae to give an approximate range of exposure in patient-years for the minimum and maximum daily dose:

$$\text{Patient exposure (patient-years)} = \frac{(\text{number of capsules sold} \times \text{capsule strength of 10 mg}) + (\text{number of capsules sold} \times \text{capsule strength of 25 mg})}{365}$$

$$\text{Patient exposure to estimated minimum daily dose of 30 mg (patient-years)} = \frac{(\text{number of capsules sold} \times \text{capsule strength of 10 mg}) + (\text{number of capsules sold} \times \text{capsule strength of 25 mg})}{365 \times 30}$$

$$\text{Patient exposure to estimated minimum daily dose of 100 mg (patient-years)} = \frac{(\text{number of capsules sold} \times \text{capsule strength of 10 mg}) + (\text{number of capsules sold} \times \text{capsule strength of 25 mg})}{365 \times 100}$$

2.5.1.2 Exposure

The cumulative global post-marketing patient exposure to KOSELUGO (10 mg and 25 mg), since launch to 31 March 2024, has been estimated to be approximately between 25,778 patient-years (based on the maximum estimated daily dose of 100 mg) and 85,925 patient-years (based on the minimum estimated daily dose of 30 mg).

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on the mechanism of action, lack of stimulant and addictive properties, selumetinib is not anticipated to have potential for misuse for illegal purposes.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

The content of this Section 2.7.1 presents the position at the time of the initial RMP for capsule formulation (Version 1), it will not be updated.

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reasons for not including an identified or potential risk in the list of safety concerns in the RMP are laid out below.

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Dry mouth
- Dry skin
- Vision blurred
- Hypoalbuminaemia
- Haemoglobin decreased (includes MedDRA PT of anaemia)
- Blood creatinine increased

Known risks that do not impact the risk-benefit profile (based on severity and seriousness)

- Asthenia (includes MedDRA Preferred Terms [PTs] of fatigue, asthenia)
- Pyrexia
- Hair changes (includes MedDRA PTs of alopecia, hair colour change)
- Peripheral oedema (includes MedDRA PTs of oedema peripheral, oedema,
- Oedema (includes MedDRA PTs of oedema peripheral, oedema, periorbital oedema, face oedema)
- Dyspnoea
- Rash (includes MedDRA PTs of dermatitis acneiform, rash maculo-papular, rash papular, rash erythematous and rash macular)
- Paronychia
- Diarrhoea
- Nausea
- Vomiting
- Stomatitis (oral mucositis)

Potential risks for which there is no anticipated exposure:

Embryo foetal toxicity

There have been few reports of pregnancy with selumetinib in adult monotherapy clinical studies in cancer indication. No abnormal birth outcomes were reported. There have been no reports of pregnancy in paediatric clinical studies.

Selumetinib is not recommended for use in women of child bearing potential who are not using contraception, warnings and precautions are provided in Section 4.4 and Section 4.6 of the SmPC advising women of child bearing potential to use contraception and avoid becoming pregnant whilst using selumetinib. Pregnancy testing is recommended prior to initiating treatment.

Other marketed MEK inhibitors (eg, trametinib) include similar warnings in their labels to avoid pregnancy during treatment.

Embryo foetal toxicity is not considered an important potential risk in the context of the definitions for inclusion in the RMP as outlined in GVP Module V revision 2. There is a very low likelihood of unplanned pregnancy in paediatric patients with NF1 who have symptomatic, inoperable PN due to the fact that paediatric patients will be under specialist care and will be made aware of the need to avoid unplanned pregnancy due to transmission risk of underlying disease (NF1 is a fully penetrant autosomal dominant genetic disorder and a person with the disease has a 50% chance of having a child with NF1). Considering this and the clear warnings in the SmPC recommending that females of child bearing potential use contraception and avoid becoming pregnant whilst using selumetinib, it is anticipated that events of pregnancy whilst on treatment will be extremely rare. This event does not therefore impact benefit risk and there is no reasonable expectation that this risk could be characterised further by pharmacovigilance activities.

Class effects:

Hypertension

Hypertension is a class effect and increased blood pressure is an adverse drug reaction (ADR) in the selumetinib SmPC. Although increases in systolic and diastolic blood pressure have been reported, changes from baseline were generally small (CTCAE grade 1 or 2) and asymptomatic. As the observed blood pressure changes are not considered to be clinically meaningful and can be effectively monitored and managed, this risk is not considered to impact the benefit risk of the product.

Haemorrhage

Bleeding events have been observed in clinical studies with selumetinib. Epistaxis was the most commonly-reported bleeding event for paediatric patients, reported in (29.6%) of patients in the paediatric pool. All reports were CTCAE Grade 1. In addition, 4 patients in the paediatric pool reported other bleeding events (AEs of lower GI haemorrhage, mouth haemorrhage, anal haemorrhage and rectal haemorrhage). With the exception of 1 AE of rectal haemorrhage, which was CTCAE Grade 2, all haemorrhage events were CTCAE Grade 1. Mouth haemorrhage was the only event that was not causally attributed by the investigator to selumetinib (attributed to the cystic plexiform in the mouth). Small, fluctuating clinically insignificant decreases from baseline in median values for platelets were observed with selumetinib treatment in the paediatric pool and this was consistent with observations in adult studies. To date, the decreases observed have not been associated with bleeding events. In the adult monotherapy pool, bleeding events were reported in (7.2%) of patients and were mostly CTCAE Grade 1 (4.9%).

Clinical data for selumetinib does not suggest that haemorrhage is an important risk in the proposed indication.

Haemorrhage is an ADR reported for other MEK inhibitors that are used in combination with BRAF inhibitors, as well as with trametinib monotherapy in the adult cancer population. Major haemorrhagic events and fatal haemorrhages have occurred in patients taking trametinib as monotherapy, with patients with brain metastases being considered at higher risk of fatal intracranial haemorrhage.

Interstitial lung disease/pneumonitis

The class effects of interstitial lung disease (ILD) and pneumonitis have not been reported with selumetinib in adult monotherapy studies in cancer or in paediatric studies in the NF1 population and these are not, therefore, considered to be safety concerns for selumetinib. The importance of these ADRs for other MEK inhibitors is increased due to the underlying condition and comorbidities of the populations being treated, which is not applicable to selumetinib in the target population. Although reported rarely for other MEK inhibitors, adult patients with cancer who develop ILD or pneumonitis may be at greater risk for developing serious respiratory toxicity. As there are no indicators of respiratory dysfunction in patients treated with selumetinib, and the target indication is not pre-disposing risk factor, ILD or pneumonitis is not considered a safety concern for inclusion in the RMP.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk

Left ventricular ejection fraction (LVEF) reduction

Risk benefit impact:

LVEF reduction is a class effect seen with other MEK inhibitors. Asymptomatic LVEF reduction, identified on ECHO assessments, has been seen in paediatric and adult patients taking selumetinib.

Left ventricular ejection fraction is the most widely accepted indicator of LV systolic function and impairment in LVEF is associated with cardiovascular outcomes. Asymptomatic LVEF reduction may progress and become symptomatic with adverse clinical outcomes such as hypotension, dyspnoea and syncope, which can be serious or life-threatening for patients.

Important Potential Risk

Physeal dysplasia

Risk benefit impact:

Mechanistically there is a plausible rationale for anticipating an effect of MEK inhibition on bone. Microscopic findings in the femoro-tibial joint (physeal dysplasia; decreased cellularity in the bone marrow femur adjacent to the physis) were reported in a 3 month study of rats at a dose of 11 times the clinical dose; 6-month dog/monkey study did not result in physeal dysplasia, and signs or symptoms of physeal dysplasia have not been reported in paediatric patients in SPRINT. Physeal dysplasia has the potential to significantly impact skeletal growth in children.

Ocular toxicity

Risk benefit impact:

Ocular toxicity is a class effect for MEK inhibitors. Vision blurred is a common ADR for selumetinib in paediatric and adult patients who received selumetinib monotherapy. Although isolated episodes of serious ocular toxicities such as retinal vein occlusion, central serous retinopathy and retinal pigment detachment events were reported in adult patients with advanced cancer, no such events were reported in the paediatric pool. However, a single event of RPED was reported in a paediatric patient receiving selumetinib monotherapy for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study.

Serious ocular toxicities can present with a range of visual disturbances, including sudden loss of sight or blindness, which constitutes ophthalmological emergency. If such events are confirmed as ADRs for paediatric patients then it would have an impact on the benefit risk balance for selumetinib.

Myopathy

Risk benefit impact:

Elevation of creatine phosphokinase (CPK), which may accompany and/or herald the onset of myopathy (including the serious outcome of rhabdomyolysis), is a very common event for MEK inhibitors although it is usually not associated with any symptoms or clinical consequences. Creatine phosphokinase increased is a very common ADR for selumetinib in the paediatric pool, but there are only a small number of reported muscle AEs, all with more plausible aetiologies than selumetinib. No reports of rhabdomyolysis were received for paediatric patients in SPRINT.

Myopathy can present with a range of clinical symptoms including myalgia, myositis and the more severe, potentially fatal event of rhabdomyolysis. These events, if confirmed, have the potential to impact the benefit risk balance for selumetinib.

Hepatotoxicity

Risk benefit impact:

Transaminase elevations are very commonly reported events for approved MEK inhibitors and elevations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been reported in paediatric patients taking selumetinib; however, adverse events suggestive of hepatotoxicity have not been observed. Elevated ALT and AST are included as a very common ADR in the selumetinib SmPC.

Drug-induced elevation of liver enzymes may be mild and transient with subsequent adaptation or may progress to more serious hepatotoxicity associated with the serious clinical outcomes of jaundice and other symptoms of hepatic failure.

Choking on the capsule

Risk benefit impact:

Some patients have difficulty swallowing medication. Selumetinib is indicated in paediatric patients from 3 years of age and older. Although there is no evidence that patients have experienced choking on the capsule, there is a potential risk that very young patients or patients with head and neck PN which may impact swallowing, could be at risk from choking on the capsule. In general, risks relating to choking and adverse swallow events have been shown to be influenced by a child's demeanour prior to, and at the time of, taking a medicine. Choking events could include gagging, coughing or vomiting or could result in airflow obstruction and collapse which could be life-threatening.

Missing Information: Long-term exposure (including long-term safety data on developmental toxicity in children)

Risk benefit impact:

Long-term effects of drug treatment in children could include impact on development, growth, and/or maturation of organ/system function. Although events indicative of long-term toxicity have not been identified to date with selumetinib, it is anticipated that selumetinib will be prescribed long-term and therefore it is important to understand what adverse effects could develop in the context of long-term dosing.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

None.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

Important identified risk

Left ventricular ejection fraction reduction

Potential mechanisms:

The effects of MEK inhibition on cardiac function can be anticipated, considering the relevance of the mitogen-activated protein kinase (MAPK) pathway in the heart. The MAPK signalling pathways in cells, including cardiac myocytes, consist of a sequence of successively acting kinases that ultimately result in the phosphorylation and activation of terminal kinases including extracellular signal related kinase (ERK) 1 and 2. The MAPK signalling cascade, once initiated in cardiac myocytes, activates a wide array of intracellular targets through phosphorylation, including transcription factors, resulting in reprogramming of cardiac gene expression (Purcell 2007).

Selumetinib is highly selective for MEK1/2 and hence, may directly suppress ERK1/2 activation in the heart. ERK1/2 has well-documented cardioprotective effects and mice genetically lacking ERK1/2 show normal cardiac phenotype under rest, but high susceptibility for stressors, such as ischaemia or pressure overload with larger infarction areas and accelerated transition from hypertrophy to heart failure (Banks 2017, Braumann 2018).

Evidence source(s) and strength of evidence:

In both paediatric and adult populations taking selumetinib, reversible, asymptomatic reductions in LVEF have been recorded in a small number of patients. LVEF reduction (corresponding MedDRA PT: ejection fraction decreased) is included as an ADR in Section 4.8 of the SmPC for selumetinib.

Characterisation of the risk:

LVEF reductions from baseline have been observed in paediatric patients in the NF1-PN paediatric and adult capsule pools. All case reports of ejection fraction decreased in the SPRINT studies were identified during routine investigations and were reported as AEs but were not associated with symptoms suggestive of cardiac failure/impairment, such as oedema, dyspnoea, palpitations, fatigue or syncope. In general, case reports of ejection fraction decreased did not result in selumetinib dose modification or discontinuation in the paediatric pool. There were no reported AEs of LVEF reduction or left ventricular systolic dysfunction in the SPRINKLE study.

Table 2-10 provides a summary of AEs of LVEF reduction per the respective safety pools.

Table 2-10 Summary of AEs of LVEF reduction

Variable		NF1-PN paediatric capsule pool (N = 126)	NF1-PN adult capsule pool (N = 153)	Adult monotherapy pool (N = 347)
		n (%)		
Frequency	Any AE	26 (20.6)	10 (6.5)	4 (1.2)
	SAE	0	0	0
Severity [a]	Mild	0	1 (0.7)	4 (1.2)
	Moderate	25 (19.8)	8 (5.2)	0
	Severe	1 (0.8)	1 (0.7)	0
Outcome [b]	Fatal	0	0	0
	Resolved	20 (15.9)	7 (4.6)	0
	Resolving	1 (0.8)	0	0
	Resolved with sequelae	0	0	0
	Not resolved	1 (0.8)	3 (2.0)	4 (1.2)
	Unknown	4 (3.2)	0	0

Note: In the SPRINT studies (coordinated by NCI, sponsored by CTEP), all echocardiogram abnormalities were reported as AEs. In other AstraZeneca-sponsored studies included in the NF1-PN paediatric and adult capsule pools, echocardiogram abnormalities were only reported as AEs when they met SAE criteria, resulted in discontinuation, or were considered clinically relevant as judged by the Investigator.

[a] If a patient has the same event more than once then the severity of the most severe event is counted.
[b] If a patient has the same event more than once then the worst case outcome is counted.
AE, adverse event; CTEP, Cancer Therapy Evaluation Program; LVEF, left ventricular ejection fraction; NCI, National Cancer Institute; NF1, neurofibromatosis type 1; SAE, serious adverse event.

Risk factors and risk groups:

In the paediatric and adult patients with NF1-PN, no specific risk factors have been identified to predict, which patients might develop LVEF reductions. It could be anticipated that patients with pre-existing impaired left ventricular function may be at greater risk of developing LVEF reductions.

Preventability:

In general, reductions in LVEF have resolved without dose modification or discontinuation in patients in the NF1-PN paediatric and adult capsule pools.

The selumetinib SmPC includes information in Section 4.4 to recommend evaluation of LVEF by echocardiogram before initiation of treatment to establish baseline values, and at approximately 3-month intervals, or more frequently as clinically indicated, during treatment. In Section 4.2 of the SmPC dose modification advice is provided to allow management of LVEF reductions.

Impact on the risk-benefit balance of the product:

Asymptomatic LVEF reduction may progress and become symptomatic with serious or life-threatening symptoms of heart failure such as hypotension, dyspnoea, oedema and syncope. Careful monitoring, early recognition and timely intervention by withholding/discontinuing selumetinib and instituting appropriate medical intervention is required to prevent or reduce the impact of this event if it occurs.

Public health impact

As the impact is to the treated population only there is no public health impact.

Important potential risks

Physeal dysplasia

Potential mechanisms:

An increase in the number of hypertrophied chondrocytes in the rodent growth plate has been associated with the administration of a number of drugs, and this pathological syndrome has been referred to as 'growth plate (physeal) dysplasia' (Brown et al 2005, Frazier et al 2007, Hall et al 2006). This change has also been described in cynomolgus monkeys administered an anti- vascular endothelial growth factor (VEGF) antibody (Ryan et al 1999) confirming translation of the effect across nonclinical species.

Reports of growth plate changes in patients have been described in a paediatric Phase I/II study of vandetanib (Bender et al 2011) a VEGF inhibitor associated with physeal dysplasia in rodents, suggesting that drugs causing physeal dysplasia in rodents have the potential to translate to man. The role of MEK inhibition in the widening of the zone of hypertrophic chondrocytes and in delayed formation of primary ossification centres in the long bone has been demonstrated in genetically engineered mouse models (Matsushita and Murakami 2012). Therefore, the bone effects in these models are consistent with the primary pharmacology of selumetinib. Based on experience with anti-angiogenic drugs (Bender et al 2011, Hall et al 2006), physeal dysplasia is considered reversible.

The trametinib SmPC states that in rats, hypertrophy of the physis and increased bone turnover were observed; however, it was not expected to be clinically relevant for adult humans.

Evidence source(s) and strength of evidence:

Mechanistically there is a plausible rationale for anticipating an effect on bone, and physeal hypertrophy is described pre-clinically for the MEK inhibitor trametinib. Preclinical evidence of physeal dysplasia following selumetinib administration at very high multiples of the clinical exposure (11 times the clinical free systemic exposure, 60 times the clinical total exposure) has been identified in the rat (however, not in the mouse or monkey) as described in module SII Non-Clinical Part of the Safety Specification.

Characterisation of the risk:

There were no case reports of AEs suggestive of physeal dysplasia in the NF1-PN paediatric capsule pool or the SPRINKLE study.

Risk factors and risk groups:

Physeal dysplasia can occur whilst the growth plate remains open and this reflects the period of risk for paediatric patients. In humans the growth plate is open from birth and closure occurs at or prior to adulthood. Limb shortening (dwarfism) and joint pain are common clinical manifestations associated with physeal dysplasia.

Preventability:

Early identification of the signs and symptoms of physeal dysplasia and timely intervention can mitigate the impact of this condition. Early identification is possible through careful monitoring, including physical assessments, height, weight, BSA, growth curve measurements and x-rays as clinically indicated.

Impact on the risk-benefit balance of the product:

Physeal dysplasia, if shown to occur clinically in association with selumetinib, could significantly impact skeletal growth in children, whose epiphyseal plates remain open. If events suggestive of physeal dysplasia are identified as an ADR, specific monitoring would need to be recommended so that treatment could be withdrawn or delayed.

Public health impact

As the impact is to the treated population only there is no public health impact.

Ocular toxicity

Potential mechanisms:

The MAPK signalling pathway, including MEK, plays a critical role in maintaining the integrity of the retinal pigment epithelium (RPE) by protecting against various stresses, including oxidative stress, light-induced damage and inflammation. Prior preclinical studies showed that MEK inhibition leads to acute RPE toxicity which results in RPE hyperpermeability and breakdown of the retinal-blood barrier (Stjepanovic et al 2016). The mechanism of MEK inhibitors in relation to RVO is poorly understood. In a study where rats were administered a MEK inhibitor and retinal gene expression was analysed, the authors hypothesised that MEK inhibitors result in changes to oxidative stress and pro-thrombotic state, which together increases the risk for RVO (Huang et al 2009). However, this is a single study and no other supporting literature has been identified.

Evidence source(s) and strength of evidence:

Ocular toxicity is a class effect for MEK inhibitors. Although blurred vision has been reported as a common event and is considered an ADR for selumetinib in the paediatric population, no serious ocular toxicities, such as RVO, central serous retinopathy (CSR; chorioretinopathy) or retinal pigment epithelial detachment (RPED), were reported for any patient in the NF1-PN paediatric and adult capsule pools or in the SPRINKLE study. However, a single event of RPED was reported in a paediatric patient receiving selumetinib monotherapy for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study. In adult patients with advanced cancer, isolated episodes of ocular toxicity (RVO in 1 patient; chorioretinopathy and RPED in 2 patients each) were reported and for this reason, ocular toxicity is considered to be an important potential risk for the paediatric population treated with selumetinib.

Characterisation of the risk:

There were no case reports of ocular toxicities, such as RVO, RPED or chorioretinopathy for any patient in the NF1-PN paediatric and adult capsule pools or the SPRINKLE study.

Risk factors and risk groups:

No case reports of ocular toxicities, such as RVO, RPED or chorioretinopathy, have been identified in the paediatric and adult patients treated with selumetinib in the NF1-PN paediatric and adult capsule pools or the SPRINKLE study and therefore, the risk factors have not been identified. Patients were excluded from taking part in the SPRINT studies, if they had a range of ophthalmologic conditions that could predispose to ocular toxicities and so it cannot be confirmed if clinically predisposing factors for ocular toxicities result in an increased risk for developing RVO, RPED or chorioretinopathy on treatment with selumetinib.

In a retrospective analysis of patients who experienced RVO in a Phase I study with an investigational MEK inhibitor, it was noted that predisposing factors for retinopathy (hypertension, diabetes, hypercholesterolaemia and glaucoma) were present in all patients with RVO; however, these predisposing factors were not confirmed prospectively (LoRusso 2010).

In accordance with the Royal College of Ophthalmologists RVO clinical guidelines (The Royal College of Ophthalmologists 2022), conditions that cause systemic inflammation or hyperviscosity increase the risk of venous thromboembolism and can rarely be associated with a RVO.

Preventability:

In general, prevention of ocular toxicities, such as RVO, RPED or chorioretinopathy, is ensured through careful monitoring, early detection, and appropriate medical intervention, following the onset of visual disturbance or retinal changes. For selumetinib, if patients report new visual disturbances, a complete ophthalmological assessment is recommended. Sections 4.2 and 4.4 of the selumetinib SmPC advise that retinal toxicities can be managed using treatment interruption, dose reduction or treatment discontinuation.

Impact on the risk-benefit balance of the product:

Ocular toxicities, such as RVO, RPED or chorioretinopathy, present with a range of visual disturbances, including sudden loss of sight or blindness, which constitutes ophthalmological emergency. As such, this has the potential to impact the risk-benefit balance of the product.

Public health impact

As the impact is to the treated population only there is no public health impact.

Myopathy

Potential mechanisms:

The RAS/RAF/MEK (MAPK/ERK) pathway is at the centre of muscle signalling networks (Lawlor 2000). Therefore, a direct role of MEK inhibition in CPK elevation and the more serious clinical manifestations of myopathy, cannot be excluded although the mechanism, by which this occurs, has not been elucidated. It is hypothesised that MEK inhibition might mitigate upstream signalling that could impair fatty acid uptake, possibly leading to muscle fatigue and weakness (Kramer 2007).

Evidence source(s) and strength of evidence:

CPK increased is listed as a very common ADR in Section 4.8 of selumetinib SmPC; however, in the paediatric and adult pools, there was no evidence of muscular AEs such as myalgia or muscular weakness in association with selumetinib-induced CPK increase, with the exception of a small number of reports where, in most cases, other more plausible aetiologies were identified. Furthermore, no events of hypocalcaemia were associated with events suggestive of muscle injury.

Elevation of CPK, which may accompany and/or herald the onset of myopathy (including the serious outcome of rhabdomyolysis), is a very common event for MEK inhibitors and is considered a class effect, although it is usually not associated with any symptoms or clinical consequences. Dropped head syndrome is a rare but distinctive myopathy that has been

described with MEK inhibition and is fully reversible with discontinuation of the MEK inhibitor (Chen et al 2012). Rhabdomyolysis is listed as an uncommon ADR for trametinib monotherapy in the SmPC.

Characterisation of the risk:

There were no case reports of myopathy in the NF1-PN paediatric and adult capsule pools and the SPRINKLE study except for one event of rhabdomyolysis in Study 11, which upon review was not consistent with a diagnosis of rhabdomyolysis. However, asymptomatic increases in CPK (corresponding MedDRA PT: creatine phosphokinase increased), which could lead to the clinical outcome of myopathy, have been observed in the NF1-PN paediatric and adult capsule pools and the SPRINKLE study. The data observed in SPRINKLE was consistent with the NF1-PN paediatric capsule pool (refer to Table 2-11).

Table 2-11 Summary of AEs of increase in creatine phosphokinase

Variable		NF1-PN paediatric capsule pool (N = 126)	NF1-PN adult capsule pool (N = 153)	Adult monotherapy pool (N = 347)
		n (%)		
Frequency	Any AE	75 (59.5)	57 (37.3)	2 (0.6)
	SAE	3 (2.4)	0	0
Severity [a]	Mild	45 (35.7)	31 (20.3)	1 (0.3)
	Moderate	22 (17.5)	17 (11.1)	0
	Severe	8 (6.3)	9 (5.9)	1 (0.3)
Outcome [b]	Fatal	0	0	0
	Resolved	69 (54.8)	27 (17.6)	0
	Resolved with sequelae	0	0	0
	Resolving	3 (2.4)	5 (3.3)	0
	Not resolved	2 (1.6)	25 (16.3)	2 (0.6)
	Unknown	1 (0.8)	0	0

Note: In the SPRINT studies (coordinated by NCI, sponsored by CTEP), all laboratory abnormalities were reported as AEs. In other AstraZeneca-sponsored studies included in the NF1-PN paediatric and adult capsule pools, laboratory abnormalities were only reported as AEs when they met SAE criteria, resulted in discontinuation, or were considered clinically relevant as judged by the Investigator.

[a] If a patient has the same event more than once then the severity of the most severe event is counted.

[b] If a patient has the same event more than once then the worst case outcome is counted.

AE, adverse event; CTEP, Cancer Therapy Evaluation Program; NCI, National Cancer Institute; NF1, neurofibromatosis type 1; SAE, serious adverse event.

Risk factors and risk groups

Since no cases of myopathy that appear drug-related have been reported in the paediatric and adult population it is not possible to identify potential risk factors for this occurrence on selumetinib. For drug-induced myopathy in general, many publications report on risk factors for statin induced myopathy which included genetic factors as well as advanced age, small body mass index, female gender, metabolic co-morbidities, and vigorous physical exercise. Age is a particularly strong contributor; however, it is unknown if these risk factors apply to MEK inhibitors and paediatric patients (Feng 2012).

Preventability

Myopathy is difficult to prevent unless specific risk factors for its development or a dose dependent relationship is identified. Other drugs where myopathy is an identified risk, recommend dose adjustment/interruption following symptomatic CPK elevation or muscle-related AEs to avoid myopathy from occurring or reduce the seriousness of symptoms.

Impact on the risk-benefit balance of the product:

Myopathy can present with a range of clinical symptoms, including myalgia, myositis, and rhabdomyolysis. Rhabdomyolysis represents the least frequent, though potentially fatal complication, caused by skeletal muscle breakdown, which leads to the release of toxic intracellular constituents into the circulation and eventually can cause acute renal failure.

Public health impact

As the impact is to the treated population only there is no public health impact.

Hepatotoxicity

Potential mechanisms:

Selumetinib is metabolised in the liver largely through the cytochrome P450 (CYP) system. CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. Serum liver enzyme elevations during selumetinib therapy have been reported clinically; however, the potential mechanism for this occurrence is not well understood.

Evidence source(s) and strength of evidence:

Elevations of ALT and AST have been reported in paediatric and adult patients and are included with a frequency of very common in Section 4.8 of the selumetinib SmPC. Transaminase elevations are also very commonly reported events for approved MEK

inhibitors. Since the mechanism is poorly understood, it cannot be ruled out that elevated transaminases may be a prelude to more serious hepatotoxicity such as liver injury.

Characterisation of the risk:

There were no case reports of hepatotoxicity, such as liver injury (including Hy's Law), in the NF1-PN paediatric and adult capsule pools, or the SPRINKLE study. However, elevations of AST and ALT, which could lead to the clinical outcome of liver injury, have been observed in the NF1-PN paediatric and adult capsule pools, and the SPRINKLE study and these are presented in Table 2-12 and Table 2-13, respectively. The data observed in SPRINKLE was consistent with the NF1-PN paediatric capsule pool.

Table 2-12 Summary of AEs of elevation of AST

Variable		NF1-PN paediatric capsule pool (N = 126)	NF1-PN adult capsule pool (N = 153)	Adult monotherapy pool (N = 347)
		n (%)		
Frequency	Any AE	46 (36.5)	27 (17.6)	17 (4.9)
	SAE	0	0	0
Severity [a]	Mild	40 (31.7)	24 (15.7)	8 (2.3)
	Moderate	4 (3.2)	2 (1.3)	4 (1.2)
	Severe	2 (1.6)	1 (0.7)	5 (1.4)
Outcome [b]	Fatal	0	0	0
	Resolved	45 (35.7)	18 (11.8)	6 (1.7)
	Resolved with sequelae	0	0	0
	Resolving	0	2 (1.3)	0
	Not resolved	1 (0.8)	7 (4.6)	11 (3.2)
	Unknown	0	0	0

Note: In the SPRINT studies (coordinated by NCI and sponsored by CTEP), all laboratory abnormalities were reported as AEs. In other AstraZeneca-sponsored studies included in the NF1-PN paediatric and adult capsule pools, laboratory abnormalities were only reported as AEs when they met SAE criteria, resulted in discontinuation, or were considered clinically relevant as judged by the Investigator.

[a] If a patient has the same event more than once then the intensity of the most severe event is counted.

[b] If a patient has the same event more than once then the worst case outcome is counted.

AE, adverse event; AST, aspartate aminotransferase; CTEP, Cancer Therapy Evaluation Program; NCI, National Cancer Institute; NF1, neurofibromatosis type 1; SAE, serious adverse event.

Table 2-13 Summary of AEs of elevation of ALT

Variable		NF1-PN paediatric capsule pool (N = 126)	NF1-PN adult capsule pool (N = 153)	Adult monotherapy pool (N = 347)
		n (%)		
Frequency	Any AE	36 (28.6)	21 (13.7)	13 (3.7)
	SAE	0	0	0
Severity [a]	Mild	33 (26.2)	17 (11.1)	7 (2.0)
	Moderate	0	3 (2.0)	3 (0.9)
	Severe	3 (2.4)	1 (0.7)	3 (0.9)
Outcome [b]	Fatal	0	0	0
	Resolved	34 (27.0)	15 (9.8)	6 (1.7)
	Resolved with sequelae	0	0	0
	Resolving	0	1 (0.7)	0
	Not resolved	0	5 (3.3)	7 (2.0)
	Unknown	2 (1.6)	0	0

Note: In the SPRINT studies (coordinated by NCI and sponsored by CTEP), all laboratory abnormalities were reported as AEs. In other AstraZeneca sponsored studies included in the NF1-PN paediatric and adult capsule pools, laboratory abnormalities were only reported as AEs when they met SAE criteria, resulted in discontinuation, or were considered clinically relevant as judged by the Investigator.

[a] If a patient has the same event more than once then the intensity of the most severe event is counted.

[b] If a patient has the same event more than once then the worst case outcome is counted.

AE, adverse event; AST, aspartate aminotransferase; CTEP, Cancer Therapy Evaluation Program; NCI, National Cancer Institute; NF1, neurofibromatosis type 1; SAE, serious adverse event.

Risk factors and risk groups

Since no reports of hepatotoxicity such as liver injury (predictable or idiosyncratic) have been received for selumetinib in the paediatric and adult population it is not possible to state what risk factors or risk groups can be identified. However, it is common for paediatric patients with NF1 to be administered medications such paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) for management of tumour pain that could place them at a higher propensity to develop hepatic events. In the literature, there are a number of risk factors for developing drug induced liver injury (DILI) that have been reported for other drugs including older age, female gender, comorbid disease and concomitant medications as well as genetic polymorphism of enzymes and proteins linked to the metabolism of drugs and overall dose of drug (Devarbhavi 2012).

Preventability:

Vigilance for symptoms and monitoring of liver functions tests is important in the detection and prevention of liver injury. The suspected drug should be stopped at the slightest suspicion of hepatotoxicity, in order to prevent progressive liver damage.

Impact on the risk-benefit balance of the product:

Elevated liver enzymes may be associated with the serious clinical outcomes of hepatotoxicity. This may be predictable (dose-related) or idiosyncratic. Clinically, it may result in severe life-threatening acute liver failure and, rarely, chronic liver disease.

Public health impact:

As the impact is to the treated population only there is no public health impact.

2.7.3.2 Presentation of missing information

Missing information

Long-term exposure (including long-term safety data on developmental toxicity in children)

Evidence source:

Selumetinib has only been given to a small number of paediatric patients for a prolonged duration in the clinical trials.

The median total duration of exposure to selumetinib in the NF1-PN paediatric capsule pool was 808 days and the maximum total duration was 2,941 days (as of the data cut-off date for each study). Fifty paediatric patients (39.7%) have received selumetinib for longer than 36 months.

The median total duration of exposure to selumetinib was 454 days in the NF1-PN adult capsule pool.

The median total duration of exposure to selumetinib was 2.1 months (maximum 14 months) in the adult monotherapy pool, with most patients (97.1%) having had < 12 months and 10 patients (2.9%) having had ≥ 12 to ≤ 24 months dosing with selumetinib.

Paediatric and adult safety data collected to date confirm that the majority of ADRs occurred in the first year of exposure and there is no indication of a worsening of the safety profile over time or the emergence of any new safety signals with long-term exposure. However, it is acknowledged that the growth and maturation of paediatric patients may result in a different safety profile over time as changes to organ systems, body mass and hormonal axes take place

and therefore, further scrutiny is necessary to observe whether AEs indicative of developmental toxicity are reported.

Population in need of further characterisation:

Paediatric patients taking selumetinib are included in the long-term follow-up assessments for the ongoing SPRINT studies (refer to Section 3.1). The ongoing post-authorisation safety study D1346R00004 will further address this missing information (refer to Section 3.2).

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

Table 2-14 Summary of safety concerns

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

3. PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

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

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

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

Other forms of routine pharmacovigilance activities:

Since selumetinib is anticipated to be prescribed for long-term use, an ongoing understanding of the safety profile following long-term exposure in the paediatric population is desirable, including impact on developmental in children. Therefore, SPRINT Phase II study was designed to carefully monitor patients for long-term tolerability to selumetinib. All patients on selumetinib treatment will have regular and ongoing safety follow-up and those who discontinue selumetinib treatment but remain on study will return annually for safety follow-up. The proposed timing for the long-term safety follow-up is 7 years following initiation of treatment or 5 years after study drug discontinuation, whichever is longer.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Post-Authorisation Safety Study (PASS)

Study short name and title:

D1346R00004 - Post-Authorisation Safety Study of Paediatric Patients Initiating Selumetinib: A Multiple-Country Prospective Cohort Study

Rationale:

To further characterise important identified and potential risks as well as missing information on long-term developmental toxicity in children.

Study objectives

Primary: To characterise the safety of selumetinib, including up to years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

Secondary: To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

Study design:

This is a cohort study of paediatric patients (aged 3 to 18 years of age) with NF1 with symptomatic, inoperable PNs who begin selumetinib treatment at study sites across several European countries where selumetinib has been marketed for use.

All patients prescribed selumetinib at the study sites will be invited to participate in the study. Patients who meet the eligibility criteria, including parental/legal guardian consent to participation, will be enrolled.

The target enrolment for the Base Cohort is 125 patients, of which approximately 100 patients are expected to meet eligibility criteria for the Nested Prospective Cohort.

The Nested Prospective Cohort is a subset of patients from the Base Cohort (aged 8 to < 18 years who have not reached Tanner Stage V on the index date). Patients in the Nested Prospective Cohort will be followed prospectively to further characterise the long-term safety of selumetinib. These patients will be followed from the index date to the censor date, which is defined as the earliest of the end of the 6-year study period, study withdrawal, loss to follow-up, or death. The 6-year study period is defined as a maximum of6 years from the time the first patient is enrolled (estimated time period = Q2 2022 to Q2 2028).

Study population:

Inclusion criteria

- Diagnosed with NF1 who have symptomatic, inoperable PN.
- Newly prescribed at least one dose of selumetinib.
- Aged 3 years and above, and ≤ 18 years of age on the index date.
- Informed consent (unless a country-specific waiver is obtained).

Additional inclusion criteria for nested prospective cohort

- At least 8 years old and prior to attainment of Tanner Stage V on the index date
- Informed consent.

Exclusion criteria

- Treatment with a mitogen-activated protein kinase inhibitor before the index date
- Participation in a randomised controlled trial

Milestones:

- Protocol submission: 13 August 2021
- Annual progress reports: Q3 2023, Q3 2024, Q3 2025, Q3 2026, Q3 2027
- Interim analysis: Q3 2025
- Final report: 31 March 2029

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study/ Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Post-authorisation safety study to characterise the long-term safety profile of selumetinib among paediatric patients with NF1 related PN in real world clinical practice. (Study D1346R00004) Ongoing	To characterise the long-term safety profile of selumetinib among paediatric patients with NF1-related PN in real world clinical practice.	• Left ventricular ejection fraction reduction • Physeal dysplasia • Ocular toxicity • Myopathy • Hepatotoxicity • Long-term exposure (including long-term safety data on developmental toxicity in children)	Protocol submission Annual progress reports Interim analysis Final report	13 August 2021 Q3 2023 Q3 2024 Q3 2025 Q3 2026 Q3 2027 Q3 2025 31 March 2029

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

4. PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

5. PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Left ventricular ejection fraction reduction	Routine risk communication: SmPC sections 4.2, 4.4, 4.8. Routine risk minimisation activities recommending specific clinical measures: SmPC section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of LVEF reduction.
Physeal dysplasia	None
Ocular toxicity	Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 (ADR of RVO, RPED). Routine risk minimisation activities recommending specific clinical measures: SmPC section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of events.
Myopathy	There are no routine risk minimisation activities for myopathy. Routine risk communication: for CPK increases, which may be a precursor for the clinical outcome of myopathy is outlined below: SmPC Section 4.8.
Hepatotoxicity	There is no routine risk communication for hepatotoxicity. Routine risk communication: for ALT and AST increases that may be precursors for the clinical outcome of hepatotoxicity is outlined below: SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures: SmPC section 4.4 Guidance is provided for monitoring and management (interrupting or stopping treatment) of ALT and AST increases.

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Long-term exposure (including long-term safety data on developmental toxicity in children)	None.

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

5.2 ADDITIONAL RISK MINIMISATION MEASURES

Routine risk minimisation activities as described in Section 5.1 (Part V: 1) are sufficient to manage the safety concerns of selumetinib.

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Ocular toxicity	Routine risk minimisation measures for ocular toxicity: SmPC sections 4.2, 4.4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Myopathy	Routine risk minimisation measures for myopathy: None. Routine risk minimisation measure for increases in CPK: SmPC section 4.8.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Hepatotoxicity	Routine risk minimisation measures for hepatotoxicity: None. Routine risk minimisation measures for elevations in ALT and AST: SmPC sections 4.4, 4.8	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up form Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)
Long-term exposure (including long-term safety data on developmental toxicity in children)	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: SPRINT Phase II study long-term follow-up Additional pharmacovigilance activities: Study D1346R00004 (final CSR: 31 March 2029)

CSR, clinical study report; PL, Package Leaflet; SmPC, Summary of Product Characteristics.

6. PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR KOSELUGO™ (SELUMETINIB)

This is a summary of the risk management plan (RMP) for KOSELUGO. The RMP details important risks of KOSELUGO, how these risks can be minimised, and how more information will be obtained about KOSELUGO's risks and uncertainties (missing information).

KOSELUGO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how KOSELUGO should be used.

This summary of the RMP for KOSELUGO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of KOSELUGO's RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

KOSELUGO capsules are authorised for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in adult and paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and older, while the KOSELUGO granules in capsule for opening are authorised for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 aged 1 year to less than 7 years (see respective SmPC for the full indications). It contains selumetinib (as hydrogen sulfate) as the active substance and it is given orally.

Further information about the evaluation of selumetinib's benefits can be found in KOSELUGO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage**.**

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of KOSELUGO, together with measures to minimise such risks and the proposed studies for learning more about selumetinib's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.

- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of selumetinib is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of KOSELUGO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of KOSELUGO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 6-1 List of important risks and missing information

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

6.2.2 Summary of important risks

Table 6-2 Important identified risk: Left ventricular ejection fraction reduction

Evidence for linking the risk to the medicine	In both paediatric and adult populations taking selumetinib, reversible, asymptomatic reductions in LVEF have been recorded in a small number of patients. LVEF reduction (corresponding MedDRA PT: ejection fraction decreased) is included as an ADR in Section 4.8 of the SmPC for selumetinib.
Risk factors and risk groups	In the paediatric and adult patients with NF1-PN, no specific risk factors have been identified to predict which patients might develop LVEF reductions. It could be anticipated that patients with pre-existing impaired left ventricular function may be at greater risk of developing LVEF reductions.
Risk minimisation measures	Routine risk minimisation measures for LVEF reduction (corresponding MedDRA PT: ejection fraction decreased): SmPC Section 4.2, 4.4, 4.8. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study D1346R00004 See Section 6.2.3 of this summary for an overview of the post authorisation development plan.

ADR, adverse drug reaction; LVEF, left ventricular ejection fraction; MedDRA, Medical Dictionary for Regulatory Activities; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; PT, preferred term; SmPC, Summary of Product Characteristics.

Table 6-3 Important potential risk: Physeal dysplasia

Evidence for linking the risk to the medicine	Mechanistically there is a plausible rationale for anticipating an effect on bone, and physeal hypertrophy is described pre clinically for the MEK inhibitor trametinib. Preclinical evidence of physeal dysplasia following selumetinib administration has been identified in the rat (however, not in the mouse or monkey).
Risk factors and risk groups	Physeal dysplasia can occur whilst the growth plate remains open and this reflects the period of risk for paediatric patients. In humans the growth plate is open from birth and closure occurs at or prior to adulthood. Limb shortening (dwarfism) and joint pain are common clinical manifestations associated with physeal dysplasia.

Table 6-3 Important potential risk: Physeal dysplasia

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study D1346R00004 See Section 6.2.3 of this summary for an overview of the post authorisation development plan.

MEK, mitogen-activated protein kinase kinase; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

Table 6-4 Important potential risk: Ocular toxicity

Evidence for linking the risk to the medicine	Ocular toxicity is a class effect for MEK inhibitors. Although blurred vision has been reported as a common event and is considered an ADR for selumetinib in the paediatric and adult population, no serious ocular toxicities such as RVO, central serous retinopathy and retinal pigment epithelial detachment were reported for any patient in the NF1-PN paediatric and adult capsule pools or in the SPRINKLE study. However, a single event of RPED was reported in a paediatric patient receiving selumetinib monotherapy for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study. In adult patients with advanced cancer, few isolated episodes of ocular toxicity were reported (RVO in 1 patient; chorioretinopathy and RPED in 2 patients each) and for this reason, ocular toxicity is considered to be an important potential risk for the paediatric population treated with selumetinib.
Risk factors and risk groups	No case reports of serious ocular toxicities such as RVO, central serous retinopathy and retinal pigment epithelial detachment have been identified in the paediatric and adult patients treated with selumetinib in the NF-1 PN paediatric pool and SPRINKLE study and therefore, the risk factors have not been identified. Patients were excluded from taking part in the SPRINT studies if they had a range of ophthalmologic conditions that could predispose to ocular toxicities and so it cannot be confirmed if clinically predisposing factors for ocular toxicities result in an increased risk for developing RVO, RPED or chorioretinopathy on treatment with selumetinib. In a retrospective analysis of patients who experienced RVO in a Phase I study with an investigational MEK inhibitor, it was noted that predisposing factors for retinopathy

Table 6-4 Important potential risk: Ocular toxicity

	(hypertension, diabetes, hypercholesterolaemia and glaucoma) were noted in all patients with RVO; however, these predisposing factors were not confirmed prospectively (LoRusso 2010). In accordance with the Royal College of Ophthalmologists RVO clinical guidelines (The Royal College of Ophthalmologists 2022), conditions that cause systemic inflammation or hyperviscosity increase the risk of venous thromboembolism and can rarely be associated with a RVO.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2, 4.4 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study D1346R00004 See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.

ADR, adverse drug reaction; MEK, mitogen-activated protein kinase kinase; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; RPED, retinal pigment epithelial detachment; RVO, retinal vein occlusion.

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The Royal College of Ophthalmologists. Clinical Guidelines: Retinal Vein Occlusion (RVO). Published 17 February 2022. Available from URL: https://www.rcophth.ac.uk/resources-listing/retinal-vein-occlusion-rvo-guidelines. Accessed: 11 September 2024.

Table 6-5 Important potential risk: Myopathy

Evidence for linking the risk to the medicine	CPK increased is listed as a very common ADR in Section 4.8 of selumetinib SmPC; however, in the paediatric and adult pools, there was no evidence of muscular AEs such as myalgia or muscular weakness in association with selumetinib-induced CPK increase, with the exception of a small number of reports where, in most cases, other more plausible aetiologies were identified. Furthermore, no events of hypocalcaemia were associated with events suggestive of muscle injury. Elevation of CPK, which may accompany and/or herald the onset of myopathy (including the serious outcome of rhabdomyolysis), is a very common event for MEK inhibitors and is considered a class effect although it is usually not associated with any symptoms or clinical consequences. Dropped head syndrome is a rare but distinctive myopathy that has been described with MEK inhibition and is fully reversible

Table 6-5 Important potential risk: Myopathy

	with discontinuation of the MEK inhibitor (Chen et al 2012). Rhabdomyolysis is listed as an uncommon ADR for trametinib monotherapy in the SmPC.
Risk factors and risk groups	Since no cases of myopathy that appear drug-related have been reported in the paediatric and adult population it is not possible to identify potential risk factors for this occurrence on selumetinib. For drug-induced myopathy in general, many publications report on risk factors for statin induced myopathy which included genetic factors as well as advanced age, small body mass index, female gender, metabolic co-morbidities, and vigorous physical exercise. Age is a particularly strong contributor; however, it is unknown if these risk factors apply to MEK inhibitors and paediatric patients (Feng 2012).
Risk minimisation measures	Routine risk minimisation measures for myopathy: None Routine risk minimisation measures for increases in CPK: SmPC section 4.8 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study D1346R00004 See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.

ADR, adverse drug reaction; CPK, creatine phosphokinase; MEK, mitogen-activated protein kinase kinase; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; SmPC, Summary of Product Characteristics.

Chen X, Schwartz GK, DeAngelis LM, Kaley T and Carvajal RD. Dropped head syndrome: Report of three cases during treatment with a MEK inhibitor. American Academy of Neurology 2012;79:1929-31.

Feng Q, Wilke RA and Baye TM. Individualized risk for statin-induced myopathy: Current knowledge, emerging challenges, and potential solutions. Pharmacogenomics 2012; 13(5):579-94.

Table 6-6 Important potential risk: Hepatotoxicity

Evidence for linking the risk to the medicine	Elevations of ALT and AST have been reported in paediatric and adult patients and are included with a frequency of very common in Section 4.8 of the selumetinib SmPC. Transaminase elevations are also very commonly reported events for approved MEK inhibitors. Since the mechanism is poorly understood, it cannot be ruled out that elevated transaminases may be a prelude to more serious hepatotoxicity such as liver injury.
Risk factors and risk groups	Since no reports of serious hepatotoxicity such as liver injury (predictable or idiosyncratic) have been received for selumetinib in the paediatric and adult population it's not possible to state what risk factors or risk groups can be identified. However, it is common for paediatric patients with NF1 to be administered medications such paracetamol or NSAIDs for management of tumour pain that could place them at a higher propensity to develop hepatic events. In the literature, there are a number of risk factors for developing DILI that have been reported for other drugs including older age, female gender, comorbid disease and concomitant medications as well as genetic polymorphism of enzymes and proteins linked to the metabolism of drugs and overall dose of drug (Devarbhavi 2012).
Risk minimisation measures	Routine risk minimisation measures for hepatotoxicity: None Routine risk minimisation measures for elevations in ALT and AST: SmPC sections 4.4, 4.8 Additional risk minimisation measures: None.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study D1346R00004 See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; MEK, mitogen-activated protein kinase kinase; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; NSAID, non-steroidal anti-inflammatory drug; SmPC, Summary of Product Characteristics.

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Table 6-7 Missing information: Long-term exposure (including long-term safety data on developmental toxicity in children)

Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Study D1346R00004 See Section 6.2.3 of this summary for an overview of the post-authorisation development plan.

NF1, neurofibromatosis type 1; PN, plexiform neurofibromas.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

D1346R00004 - 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.

Purpose of the study: To further characterise the important identified and potential risks as well as missing information on long-term developmental toxicity in children.

Study objectives

Primary: To characterise the safety of selumetinib, including up to 6 years of long-term safety, in paediatric patients with NF1-related symptomatic, inoperable PN, 8 to < 18 years old who have not reached Tanner Stage V at the start of selumetinib treatment (Nested Prospective Cohort).

Secondary: To describe the demographic and clinical profile of the paediatric population 3 to < 18 years old with NF1-related symptomatic inoperable PN who start selumetinib in routine clinical practice (Base Cohort).

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for KOSELUGO.

[redacted]

7.4 ANNEX 4: Specific adverse drug reaction follow-up forms

- *Physeal dysplasia targeted safety questionnaire*
- *Left ventricular ejection fraction reduction targeted safety questionnaire*
- *Ocular toxicity targeted safety questionnaire*
- *Myopathy targeted safety questionnaire*
- *Hepatotoxicity targeted safety questionnaire*

[redacted]

7.6 ANNEX 6: Details of proposed additional risk minimisation activities

Not applicable.

[redacted]

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