Summary Report of Benefit-Risk Assessment

KOSELUGO HARD CAPSULES 10MG/ 25MG

NEW DRUG APPLICATION

Active Ingredient(s)	Selumetinib
Product Registrant	ASTRAZENECA SINGAPORE PTE LTD
Product Registration Number	SIN16275P, SIN16276P
Application Route	Abridged evaluation
Date of Approval	9 July 2021

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A INTRODUCTION

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

The active substance, selumetinib, is a selective inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. Selumetinib blocks MEK activity and inhibits growth of RAF-MEK-ERK pathway activated cell lines, thus blocking the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.

Koselugo is available as hard capsules containing 10mg or 25mg of selumetinib (as hyd-sulfate) and the excipients, vitamin E polyethylene glycol succinate, and hypromellose.

The hard capsule shell for 10 mg capsule contains hypromellose, carrageenan, potassium chloride, titanium dioxide, carnauba wax and purified water. The printing ink for the 10mg capsule comprises iron oxide black (E 172), propylene glycol, shellac glaze and ammonium hydroxide 28%.

The hard capsule shell for 25 mg capsule contains hypromellose, carrageenan, potassium chloride, titanium dioxide, FD&C Blue 2 (E 132), ferric oxide yellow (E 172), purified water, carnauba wax and/or corn starch. The printing ink for the 25mg capsule comprises ferric oxide red (E 172), ferric oxide yellow (E 172), FD&C Blue 2 Aluminium lake (E 132), glyceryl monooleate, white shellac and carnauba wax.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, selumetinib hyd-sulfate, is manufactured at Dottikon Exclusive Synthesis AG, Dottikon, Switzerland. The drug product, Koselugo, is manufactured at Patheon Pharmaceuticals Inc, Ohio, United States.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities, including potentially genotoxic impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data presented is adequate to support the approved storage condition and re-test period. The drug substance is packed in double low-density polyethylene (LDPE) bags placed

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within a rigid outer container. The drug substance is approved for storage below 30ºC with a re-test period of 84 months.

Drug product:
The drug substance is mixed with the excipients, and subsequently filled into the hard hypromellose capsules. The process is considered a standard process.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies are conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods are validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted is adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a high-density polyethylene (HDPE) bottle with a silica gel desiccant containing 60 capsules and is able to provide protection from moisture and light.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of selumetinib for the treatment of paediatric patients aged 3 years and above with NF1 who have symptomatic, inoperable PN was based primarily on the evidence from Phase II Stratum 1 of study SPRINT.

SPRINT Phase II Stratum 1 was an open-label, single-arm, multi-centre study in paediatric patients with NF1 and inoperable PN. A total of 50 patients aged ≥2 and ≤18 years with NF1 and inoperable PN with PN-related morbidity were enrolled. Patients were required to have at least 1 measurable PN, defined as a PN of at least 3 cm measured in one dimension. Patients received 25 mg/m^2 twice daily (BID), for 28 days (1 treatment cycle), on a continuous dosing schedule. Treatment was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity or PN progression, or at the discretion of the investigator. Selumetinib dose was chosen based on the dose-limiting toxicity (DLT) assessment in study SPRINT Phase I. Three dose levels of selumetinib were evaluated (20, 25 and 30 mg/m^2 BID) and 1 of 6 patients had a DLT at the dose of 25 mg/m^2 BID. The 25 mg/m^2 BID dose was determined as the maximum tolerated dose and used in Phase II of the study.

The primary efficacy endpoint was objective response rate (ORR), defined as the percentage of patients with a complete response (CR is disappearance of the target PN) or confirmed partial response (PR is target PN volume decrease from baseline ≥20%, confirmed when documented by subsequent volumetric MRI within 3 to 6 months). Tumour response was assessed by National Cancer Institute (NCI) Pediatric Oncology Branch (POB) central analysis using volumetric magnetic resonance imaging (MRI) analysis per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. The secondary efficacy endpoints included duration of response (DoR), time to response (TTR), and progressive free survival (PFS).

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The median age of patients at enrolment was 10.2 years (range: 3.5 to 17.4 years). The majority of patients were Caucasian (84.0%) and male (60.0%). At baseline the median target PN volume was 487.5 mL. There were 42.0% of patients who were classified as having a progressive target PN (i.e. growth ≥20% in the 12 to 15 months prior to enrolment), and 30.0% had a non-progressive target PN. No classification was available for the remaining patients. Patients had a median number of 3 morbidities present at baseline, with approximately a quarter of patients (13 patients) having 4 morbidities assigned to their target PN. The most common PN-related baseline morbidities were disfigurement (88.0%), motor dysfunction (66.0%), pain (52.0%) and airway dysfunction (32.0%).

Selumetinib demonstrated a confirmed ORR of 66.0% (95% CI: 51.2 to 78.8) by NCI POB central analysis. Similar ORR (61.9%) was observed in patients with progressive PN at baseline, suggesting that PN status at baseline appeared to be independent from response rate and therefore not predictive of selumetinib efficacy. The median TTR was 8.0 cycles while the median DoR from onset of response was not reached. Of the 33 responders, the probability of remaining in response after 12 cycles and 16 cycles, estimated using the Kaplan-Meier method, was 100% (95% CI not estimated) and 96.2% (95% CI: 75.7 to 99.4), respectively. Three patients had progressed at data cut-off and median PFS was not reached.

Supporting evidence were based on study SPRINT Phase I. This was an open-label, single-arm, dose-escalation, multi-centre study in paediatric patients with NF1 inoperable PN. A total of 24 patients aged ≥3 and ≤18 years with at least 1 measurable PN were enrolled. Twelve patients received selumetinib 20 mg/m^2 BID, 6 patients received selumetinib 25 mg/m^2 BID and 6 patients received selumetinib 30 mg/m^2 BID. The median age at enrolment was 10.9 years (range: 3.0 to 18.5 years). The majority of patients were Caucasian (75.0%) and male (54.2%). At baseline the median target PN volume was 1204.5 mL (range: 29.4 to 8744.0 mL). Of the 24 patients,16 were confirmed responders (ORR 66.7%) and maintained in response after 16 cycles from the onset of response. The median TTR was 7.5 cycles while the median DoR from onset of response was not reached. After 52 cycles, the estimated proportion of patients remaining in response based on Kaplan-Meier analysis was 100%. Two patients had progressed and the median PFS was not reached.

Summary of key efficacy results (SPRINT Phase I and Phase II Stratum 1, FAS)

Efficacy Parameter	Phase II, Stratum 1 (N = 50)	Phase I (N=24)
Objective Response Rate		
Objective Response Rate, % (95% CI)	66.0 (51.2 – 78.8)	66.7 (44.7 – 84.4)
Best objective response, n (%)		
Complete Response	0	0
Confirmed Partial Response	33 (66%)	16 (66.7%)
Unconfirmed Partial Response	4 (8%)	2 (8.3%)
Stable Disease	11 (22%)	5 (20.8%)
Progressive Disease	0	0
Progressive free survival		
Median months	NR	NR
Time to response		
Median cycles	8	7.5
Duration of Response[a]		
Median (95% CI) months	NR (NE – NE)	NR (NE, NE)
Estimated percentage remaining in response		
After 12 cycles, % (95% CI)	100 (NE – NE)	100 (NE - NE)
After 16 cycles, % (95% CI)	96.2 (75.7 – 99.4)	100 (NE - NE)
After 52 cycles, % (95% CI)	NE	100 (NE - NE)

FAS: full analysis set, CI - confidence interval, NE – not estimated, NR - not reached

[a] Duration of Response from onset of response based on Kaplan-Meier analysis in patients with confirmed partial response.

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In view of the limitations of the open-label single-arm design of SPRINT Phase II Stratum 1, external control data from the NCI POB Natural History of NF1 (Natural History study) and the placebo control group from the historical Study 01-C-0222 were presented for comparisons.

The prospective NF1 Natural History study was conducted by the NCI POB in paediatric and adult patients with a clinical diagnosis of NF1 or a confirmed NF1 mutation to longitudinally characterise and analyse NF1-related tumour and non-tumour manifestations, and to develop a better understanding of the biology of NF1-related manifestations. Ninety-two age-matched patients who had at least 1 volumetric MRI scan between age ≥3 to ≤18 years and at least 1 subsequent volumetric MRI were analysed to provide contextual comparison with study SPRINT Phase II Stratum 1, and the data served as an external control for the endpoints of PN growth rate and PFS.

In this study, the adjusted mean annual PN growth rate was +21.3% (95% CI: +15.9, +26.8) compared to -16.9% (95% CI: -20.2, -13.5) per year in study SPRINT Phase II Stratum 1. Comparison with the age-matched cohort indicated that the PN shrinkage observed in study SPRINT Phase II Stratum 1 could be attributed to selumetinib, rather than the natural course of the disease.

Comparison of target PN growth rate, ORR and PFS in patients aged ≥3 to <18 years

Group	n	Time period years Median (min, max)	PN volume % change/ year Median (min, max)	Annual PN growth rate (95% CI)	ORR	PFS (years 95% CI)
SPRINT Phase II Stratum 1	48[a]	1.8 (0.3, 2.8)	-10.2 (-27.3, 19.0)	-16.9 (-20.2, -13.5)	66.0%	Not reached
External Control*	90[b]	2.5 (0.8, 2.8)	21.3 (-4.1, 147.9)	21.3 (15.9, 26.8)	NA	1.3 (1.1, 1.6)

*: NCI POB NF1 prospective Natural History study (age matched and aligned to maximum follow up duration of SPRINT Phase II Stratum 1)
a: Two patients were not included as they did not have any post-baseline volumetric MRI scans
b; Two patients with only 1 volumetric MRI scan within the 2.8 years were not included in the growth analysis

Study 01-C-0222 was a multi-centre, double-blinded, placebo-controlled, randomised, cross-over study of tipifarnib in children and young adults with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity. Data from 29 patients from the placebo arm of Study 01-C-0222 were compared with the subgroup of patients with progressive PN at enrolment in SPRINT Phase II Stratum 1. The PFS in study SPRINT Phase II Stratum 1 and the placebo arm of Study 01-C-0222 was presented in figure below, which demonstrates PFS benefit with selumetinib treatment compared with patients in the placebo arm Study 01-C-0222.

Kaplan-Meier plot of PFS, placebo arm of Study 01-C-0222 and SPRINT Phase II Stratum 1 (Progressive PN)

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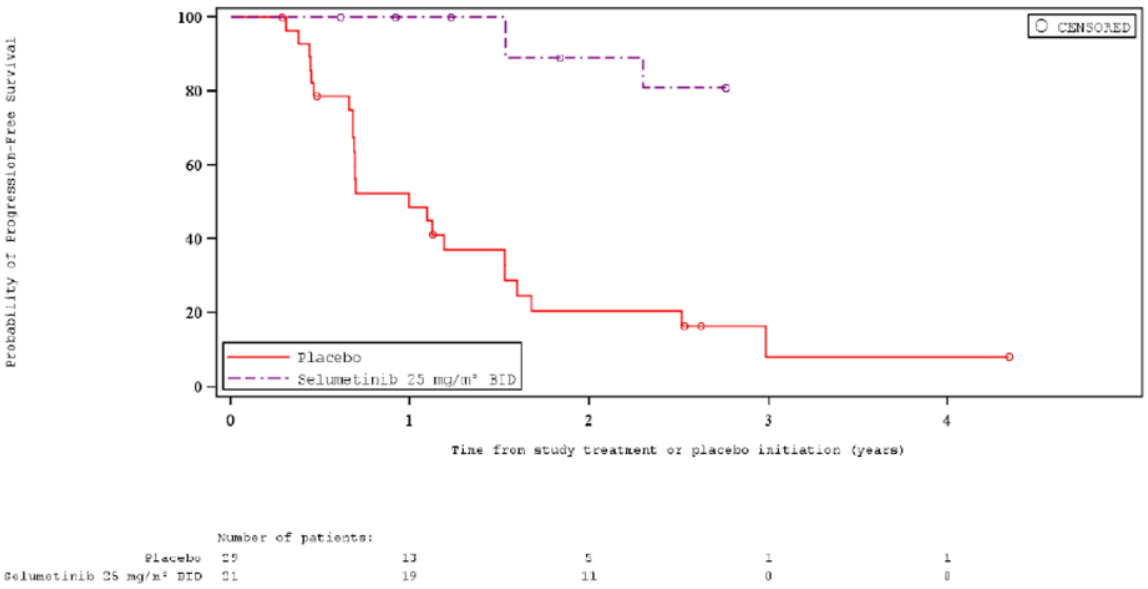

Overall, the results of study SPRINT adequately supported the efficacy of selumetinib in paediatric patients with NF1 and inoperable PN and would offer a therapeutic option for patients who are unable to undergo surgery and currently have no other treatment options.

D ASSESSMENT OF CLINICAL SAFETY

The safety of selumetinib in paediatric patients with NF1 was evaluated in SPRINT Phase II Stratum 1 comprising 50 patients who received selumetinib 25 mg/m^2 BID, and supported by the Phase I data comprising a total of 24 patients who received selumetinib 20 mg/m^2 BID (n=12), 25 mg/m^2 BID (n=6), or 30 mg/m^2 BID (n=6), as well as the Paediatric pool comprising all patients from both the Phase II and Phase I of SPRINT who received all doses of selumetinib (N=74). In study SPRINT Phase II Stratum 1, median total exposure to selumetinib was 801.5 days (range 28 to 1053 days). The median and duration of exposure in the Paediatric pool was higher than in study SPRINT Phase II Stratum 1 (855.5 days, range 28 to 2169 days) as it was influenced by the longer exposure to selumetinib in the study SPRINT Phase I data.

Overview of safety profile (SPRINT Phase II Stratum 1 and paediatric pool)

	Number (%) of patients	
AE	**SPRINT Phase II Stratum 1 25 mg/m^2 BID (N=50)**	**Paediatric pool All doses (N=74)**
Any AE	49 (98.0)	73 (98.6)
Any AE causally related to selumetinib*	49 (98.0)	73 (98.6)
SAE	12 (24.0)	17 (23.0)
Any SAE causally related to selumetinib*	6 (12.0)	8 (10.8)
Discontinuations due to AE	6 (12.0)	9 (12.2)
Deaths due to AE	0 (0)	0 (0)

*as determined by the investigator
AE: adverse event; SAE: serious adverse event

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The most frequently reported adverse events (AEs) in study SPRINT Phase II Stratum 1 (≥45.0% of patients) were: vomiting (82.0%); blood creatine phosphokinase increased (76.0%); diarrhoea (70.0%); nausea (66.0%); dry skin (60.0%); fatigue (56.0%); pyrexia (56.0%); dermatitis acneiform; hypoalbuminaemia and stomatitis (50.0%, each); headache and oropharyngeal pain (48.0%, each); aspartate aminotransferase increased, paronychia, and pruritus (46.0%, each). The incidence of AEs was generally similar in study SPRINT Phase II Stratum 1 to those from the Paediatric pool. These were consistent with events observed in a paediatric population with the underlying disease and the safety profile of MEK inhibitor drug class.

Identified risks associated with the use of selumetinib such as gastrointestinal effects (diarrhoea, nausea and vomiting), vision blurred, transaminase elevations, creatine phosphokinase increase, rash/dermatitis acneiform, left ventricular ejection fraction decrease were generally of low severity (grades 1 or 2), and were manageable with either selumetinib dose modifications and/or paediatric specific AE management guidelines/ local practice that were utilized in SPRINT study. These events did not affect the ability of patients to remain on treatment for long periods of time (for at least 4.1 years).

There were no events of physeal dysplasia, impairment in sexual maturation or retinal events noted in the Paediatric pool. In addition, the incidence of serious adverse events (SAEs) considered possibly related to selumetinib and the incidence of AEs leading to the permanent discontinuation of selumetinib treatment were generally low (10.8% and 12.2% respectively). No deaths were reported in the Paediatric pool.

Overall, selumetinib presented an acceptable safety profile for paediatric patients aged 3 to 18 years and above with NF1 and symptomatic, inoperable PN. Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

E ASSESSMENT OF BENEFIT-RISK PROFILE

NF1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene (17q11.2), which encodes the tumour suppressor protein neurofibromin 1. Patients with NF1 have an increased risk of developing tumours of the central and peripheral nervous system. PNs are one of the most common benign tumours which occur in approximately 20% to 50% of patients. Typical PNs are clinically distinct from localised (or 'nodular' or 'atypical') neurofibromas in that the latter have potential for malignant transformation and are considered by some to be pre-malignant. Currently, the only available options to treat and manage NF1 are pain management and surgical excision to remove as much of the PN as possible.

In the pivotal study, SPRINT Phase II Stratum 1, selumetinib demonstrated a confirmed ORR of 66.0% (95% CI: 51.2 to 78.8). Responses occurred early with the median TTR as 8.0 cycles. The median DoR from onset of response was not reached. Very few patients progressed (3 patients) and median PFS was not reached. Comparisons with external control data indicated that the reduction in target PN volume was attributed to selumetinib and not the natural history of the disease.

The safety profile of selumetinib was considered acceptable and consistent with the known safety profile of the MEK inhibitor drug class. Overall, the AEs were considered manageable.

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Appropriate warnings and precautions have been included in the package insert to address the identified safety risks.

On balance, the benefit-risk profile of selumetinib for the treatment of paediatric patients aged 3 years and above with NF1 who have symptomatic, inoperable PN was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Koselugo for the treatment of paediatric patients aged 3 years and above with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN) was deemed favourable and approval of the product registration was granted on 9 July 2021.

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KOSELUGO®
(selumetinib)

1. NAME OF THE MEDICINAL PRODUCT

KOSELUGO (selumetinib) 10 mg, hard capsules

KOSELUGO (selumetinib) 25 mg, hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10 mg hard capsule contains 10 mg of selumetinib (as hydrogen sulfate).

Each 25 mg hard capsule contains 25 mg of selumetinib (as hydrogen sulfate).

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

KOSELUGO 10 mg hard capsule

White to off-white, opaque, size 4 hard capsule, banded and marked with “SEL 10” in black ink.

KOSELUGO 25 mg hard capsule

Blue, opaque, size 4 hard capsule, banded and marked with “SEL 25” in black ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

The recommended dose of KOSELUGO is 25 mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours).

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

Table 1 KOSELUGO recommended dosage based on body surface area

Body surface area (BSA)[a]	Recommended Dosage
0.55 – 0.69 m^2	20 mg in the morning and 10 mg in the evening
0.70 – 0.89 m^2	20 mg twice daily
0.90 – 1.09 m^2	25 mg twice daily
1.10 – 1.29 m^2	30 mg twice daily
1.30 – 1.49 m^2	35 mg twice daily
1.50 – 1.69 m^2	40 mg twice daily
1.70 – 1.89 m^2	45 mg twice daily
≥1.90 m^2	50 mg twice daily

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

Treatment with KOSELUGO should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity.

Method of administration

KOSELUGO should be taken on an empty stomach with no food or drink other than water. Do not consume food 2 hours prior to dosing and 1 hour after dosing (see Sections 4.5 and 5.2).

KOSELUGO capsules should be swallowed whole with water, and should not be chewed, dissolved, or opened.

Missed dose

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

Vomiting

Do not take an additional dose if vomiting occurs after KOSELUGO administration but continue with the next scheduled dose.

Dose adjustments

For adverse events

Interruption and/or dose reduction or permanent discontinuation of KOSELUGO may be required based on individual safety and tolerability (see Sections 4.4 and 4.8).

Recommended dose reductions are given in Table 2 and may require the daily dose to be divided into two administrations of different strength or for treatment to be given as a once daily dose.

Table 2 KOSELUGO recommended dose reductions for adverse reactions

Body surface area (BSA)	First dose reduction (mg/dose)		Second dose reduction (mg/dose)*	
	Morning	Evening	Morning	Evening
0.55 – 0.69 m^2	10	10	10 once daily	
0.70 – 0.89 m^2	20	10	10	10

Body surface area (BSA)	First dose reduction (mg/dose)		Second dose reduction (mg/dose)*	
	Morning	Evening	Morning	Evening
0.90 – 1.09 m^2	25	10	10	10
1.10 – 1.29 m^2	25	20	20	10
1.30 – 1.49 m^2	25	25	25	10
1.50 – 1.69 m^2	30	30	25	20
1.70 – 1.89 m^2	35	30	25	20
≥1.90 m^2	35	35	25	25

* Permanently discontinue KOSELUGO in patients unable to tolerate KOSELUGO after two dose reductions.

Table 3 Recommended KOSELUGO dosage modifications for adverse reactions

CTCAE Grade*	Recommended Dose Modification
Grade 1 or 2 (tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (intolerable) or **Grade 3**	Interrupt treatment until toxicity is grade 0 or 1 and reduce by one dose level when resuming therapy (see Table 2).
Grade 4	Interrupt treatment until toxicity is grade 0 or 1, reduce by one dose level when resuming therapy (see Table 2). Consider discontinuation.

*Common Terminology Criteria for Adverse Events (CTCAE)

Dose modification advice for left ventricular ejection fraction (LVEF) reduction

In cases of asymptomatic LVEF reduction of ≥10 percentage points from baseline and below the institutional lower level of normal (LLN), KOSELUGO treatment should be interrupted until resolution. Once resolved, reduce KOSELUGO by one dose level when resuming therapy (see Table 2).

In patients who develop symptomatic LVEF reduction or a grade 3 or 4 LVEF reduction, KOSELUGO should be discontinued and a prompt cardiology referral should be carried out (see Section 4.4).

Dose modification advice for ocular toxicities

KOSELUGO treatment should be interrupted in patients diagnosed with retinal pigment epithelial detachment (RPED) or central serous retinopathy (CSR) with reduced visual acuity until resolution; reduce KOSELUGO by one dose level when resuming therapy (see Table 2). In patients diagnosed with RPED or CSR without reduced visual acuity, ophthalmic assessment should be conducted every 3 weeks until resolution. In patients who are diagnosed with retinal vein occlusion (RVO), treatment with KOSELUGO should be permanently discontinued (see Section 4.4).

Special patient populations

Renal impairment

Based on clinical studies no dose adjustment is recommended in patients with mild, moderate, severe renal impairment or those with End Stage Renal Disease (ESRD) (see Section 5.2).

Hepatic impairment

Based on clinical studies, no dose adjustment is recommended in patients with mild hepatic impairment. The starting dose should be reduced in patients with moderate hepatic impairment to 20 mg/m^2 BSA, twice daily. KOSELUGO is not recommended for use in patients with severe hepatic impairment (see Section 5.2).

Ethnicity

Increased systemic exposure has been seen in adult Asian subjects, although there is considerable overlap with Western subjects when corrected for body weight. No specific adjustment to the starting dose is recommended for paediatric Asian patients, however, these patients should be closely monitored for adverse events (see Section 5.2).

Paediatric population

The safety and efficacy of KOSELUGO in children less than 3 years of age has not been established. No data are currently available.

4.3 Contraindications

None.

4.4 Special warnings and precautions for use

Cardiomyopathy

Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) ≥10% below baseline, occurred in 23% of 74 paediatric patients who received KOSELUGO in SPRINT (see Section 4.8). Four percent of patients experienced decreased LVEF below the institutional lower limit of normal (LLN). Grade 3 decreased LVEF occurred in one patient and resulted in dose reduction. All patients with decreased LVEF were asymptomatic and identified during routine echocardiography. Decreased LVEF resolved in 71% of these patients.

Left ventricular dysfunction or decreased LVEF resulting in permanent discontinuation of KOSELUGO occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO. Decreased LVEF resulting in permanent discontinuation of KOSELUGO occurred in a paediatric population with NF1 in an expanded access program.

The safety of KOSELUGO has not been established in patients with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN.

Assess ejection fraction by echocardiogram prior to initiating treatment, every 3 months during the first year of treatment, every 6 months thereafter, and as clinically indicated. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (see Section 4.2). In patients who interrupt KOSELUGO for decreased LVEF, obtain an echocardiogram or a cardiac MRI every 3 to 6 weeks. Upon resolution of decreased LVEF to

greater than or equal to the institutional LLN, obtain an echocardiogram or a cardiac MRI every 2 to 3 months or as directed by the cardiologist.

Ocular Toxicity

Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 paediatric patients receiving KOSELUGO in SPRINT. Blurred vision resulted in dose interruption in 2.7% of patients. Ocular toxicity resolved in 82% of 11 patients.

Serious ocular toxicities including retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED), occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO as a single agent or in combination with other anti-cancer agents. RPED occurred in the paediatric population during treatment with single agent KOSELUGO and resulted in permanent discontinuation.

Conduct comprehensive ophthalmic assessments prior to initiating KOSELUGO, at regular intervals during treatment, and for new or worsening visual changes. Permanently discontinue KOSELUGO in patients with RVO. Withhold KOSELUGO in patients with RPED, follow up with optical coherence tomography assessments every 3 weeks until resolution, and resume KOSELUGO at a reduced dose. For other ocular toxicities, withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of the adverse reaction (see Section 4.2).

Gastrointestinal Toxicity

Diarrhoea occurred in 77% of 74 paediatric patients who received KOSELUGO in SPRINT, including Grade 3 in 15% of patients. Diarrhoea resulting in permanent discontinuation occurred in 1.4% of patients. Diarrhoea resulting in dose interruption or dose reduction occurred in 15% and 1.4% of patients, respectively. The median time to first onset of diarrhoea was 17 days and the median duration was 2 days.

Serious gastrointestinal toxicities, including perforation, colitis, ileus, and intestinal obstruction, occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO as a single agent or in combination with other anti-cancer agents. Colitis occurred in an unapproved population of paediatric patients with multiple tumour types who received KOSELUGO as a single agent.

Advise patients to start an anti-diarrhoeal agent (e.g., loperamide) immediately after the first episode of unformed, loose stool and to increase fluid intake during diarrhoea episodes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (see Section 4.2).

Skin Toxicity

Rash occurred in 91% of 74 paediatric patients who received KOSELUGO in SPRINT. The most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%). Grade 3 rash occurred in 8% of patients. Rash resulted in dose interruption in 11% of patients and dose reduction in 4% of patients.

Other skin toxicities, including severe palmar-plantar erythrodysesthesia syndrome, occurred in an unapproved population of adult patients with multiple tumour types who received KOSELUGO as a single agent or in combination with other anti-cancer agents.

Monitor for severe skin rashes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (see Section 4.2).

Increased Creatine Phosphokinase

Increased creatine phosphokinase (CPK) occurred in 76% of 74 paediatric patients who received KOSELUGO in SPRINT, including Grade 3 or 4 in 9% of patients. Increased CPK resulted in dose reduction in 7% of patients. Increased CPK concurrent with myalgia occurred in 8% of patients, including one patient who permanently discontinued KOSELUGO for myalgia.

Rhabdomyolysis occurred in an unapproved adult population who received KOSELUGO as a single agent.

Obtain serum CPK prior to initiating KOSELUGO, periodically during treatment, and as clinically indicated. If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce dose, or permanently discontinue KOSELUGO based on severity of adverse reaction (see Section 4.2).

Increased Levels of Vitamin E and Risk of Bleeding

KOSELUGO capsules contain vitamin E (10 mg capsules contain 32 mg vitamin E as the excipient, D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS); while KOSELUGO 25 mg capsules contain 36 mg vitamin E as TPGS). Vitamin E can inhibit platelet aggregation and antagonize vitamin K- dependent clotting factors. Daily vitamin E intake that exceeds the recommended or safe limits may increase the risk of bleeding. Supplemental vitamin E is not recommended if daily vitamin E intake (including the amount of vitamin E in KOSELUGO and supplement) will exceed the recommended or safe limits.

An increased risk of bleeding in patients may occur in patients who are coadministered vitamin-K antagonists or anti-platelet antagonists with KOSELUGO. Monitor for bleeding in these patients. Increase international normalized ratio (INR) monitoring, as appropriate, in patients taking a vitamin-K antagonist. Perform anticoagulant assessments, including INR or prothrombin time, more frequently and adjust the dose of vitamin K antagonists or anti-platelet agents as appropriate (see Section 4.5).

Embryo-Foetal Toxicity

Based on findings from animal studies and its mechanism of action, KOSELUGO can cause foetal harm when administered to a pregnant woman. In animal reproduction studies, administration of selumetinib to mice during organogenesis caused reduced foetal weight, adverse structural defects, and effects on embryo-foetal survival at approximate exposures >5 times the human exposure at the clinical dose of 25 mg/m^2 twice daily. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with KOSELUGO and for 1 week after the last dose (see Section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

Interaction studies have only been performed in healthy adults (aged ≥18 years).

Active substances that may increase selumetinib plasma concentrations

Co-administration with a strong CYP3A4 inhibitor (200 mg itraconazole twice daily for 4 days) increased selumetinib C_{max} by 19% (90% CI 4, 35) and AUC by 49% (90% CI 40, 59) in healthy adult volunteers. Concomitant use of erythromycin (moderate CYP3A4 inhibitor) is predicted to increase selumetinib AUC by 41% and C_{max} by 23%.

Co-administration with a strong CYP2C19/moderate CYP3A4 inhibitor (200 mg fluconazole once daily for 4 days) increased selumetinib C_{max} by 26% (90% CI 10, 43) and AUC by 53% (90% CI 44, 63) in healthy adult volunteers, respectively.

Avoid co-administering KOSELUGO with medicinal products that are strong inhibitors of CYP3A4 (e.g., clarithromycin, grapefruit juice, oral ketoconazole) and CYP2C19 (e.g., ticlopidine). If co-administration is unavoidable, patients should be carefully monitored for adverse events (see section 4.2).

No dose adjustment is necessary for use of KOSELUGO with moderate CYP3A4 or CYP2C19 inhibitors. Patients should be carefully monitored for adverse events when co-administered with moderate CYP3A4 or CYP2C19 inhibitors.

Active substances that may decrease selumetinib plasma concentrations

Co-administration with a strong CYP3A4 inducer (600 mg rifampicin daily for 8 days) decreased selumetinib C_{max} by -26% (90% CI -17, -34) and AUC by -51% (90% CI -47, -54). Concomitant use of efavirenz (moderate CYP3A4 inducer) is predicted to decrease selumetinib AUC by -38% and C_{max} by -22%. Avoid concomitant use of strong CYP3A4 inducers (e.g. phenytoin, rifampicin, carbamazepine, St. John's Wort) or moderate CYP3A4 inducers with KOSELUGO.

Active substances whose plasma concentrations may be altered by selumetinib

In vitro, selumetinib is an inhibitor of OAT3 and the potential for a clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 cannot be excluded (see Section 5.2).

Vitamin E

KOSELUGO capsules contain vitamin E as the excipient TPGS. Therefore, patients should avoid taking supplemental vitamin E and anticoagulant assessments should be performed more frequently in patients taking concomitant anticoagulant or antiplatelet medications (see Section 4.4).

4.6 Pregnancy and lactation

Contraception in males and females

Women of childbearing potential should be advised to avoid becoming pregnant while receiving KOSELUGO. Both male and female patients (of reproductive potential) should be advised to use effective contraception during and for at least 1 week after completion of treatment with KOSELUGO.

KOSELUGO is not recommended in women of childbearing potential not using contraception.

Pregnancy

There are no data on the use of KOSELUGO in pregnant women. Studies in animals have shown reproductive toxicity including embryofoetal death, structural defects and reduced foetal weights (see Section 5.3). KOSELUGO is not recommended during pregnancy.

It is recommended that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment.

Advise women of childbearing potential to avoid becoming pregnant while receiving KOSELUGO. If a female patient or a female partner of a male patient receiving KOSELUGO becomes pregnant, she should be apprised of the potential hazard to the foetus.

Lactation/Breast Feeding

KOSELUGO and its active metabolite are excreted in the milk of lactating mice (see Section 5.3). It is not known whether KOSELUGO, or its metabolites, are excreted in human milk. A risk to the breast-fed infant cannot be excluded, therefore breast-feeding mothers are advised not to breast-feed during treatment with KOSELUGO.

Fertility

There are no data on the effect of KOSELUGO on human fertility.

KOSELUGO had no impact on fertility and mating performance in male and female mice, although a reduction in embryonic survival was observed in female mice (see Section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Overall summary of the safety profile

The safety of KOSELUGO monotherapy has been evaluated in a combined safety population of 74 paediatric patients (20-30 mg/m^2 twice daily) with NF1 PN and 347 adult patients (75-100 mg twice daily) with multiple tumour types.

The median total duration of KOSELUGO treatment in paediatric patients with NF1 PN was 28 months (range: <1 – 71 months), 23% of patients were exposed to KOSELUGO treatment for >48 months. The safety database is supported by serious adverse event reports from 291 paediatric patients enrolled in externally sponsored studies across a range of indications.

In the Phase II Stratum 1 pivotal study (SPRINT), 50 paediatric patients with NF1 PN were treated with KOSELUGO 25 mg/m^2 twice daily, see Section 5.1. The most common adverse reactions of any grade (incidence ≥45%) were vomiting, rash, blood creatine phosphokinase increased, diarrhoea, nausea, dry skin, asthenic events, pyrexia, acneiform rash, hypoalbuminaemia, stomatitis, aspartate aminotransferase increased and paronychia. Dose interruptions and reductions due to adverse events were reported in 80% and 24% of patients, respectively. The most commonly reported ADRs leading to dose modification of KOSELUGO were vomiting (12 [24.0%]), paronychia (7 [14.0%]), diarrhoea (6 [12.0%]) and

nausea (5 [10.0%]). Permanent discontinuation due to adverse events was reported in 12% of the patients.

Tabulated list of adverse reactions

Table 4 presents the adverse reactions identified in the SPRINT Phase II Stratum 1. Adverse reactions are organised by MedDRA System Organ Class (SOC). Within each SOC, preferred terms are arranged by decreasing frequency and then by decreasing seriousness. Frequencies of occurrence of adverse reactions are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000) and not known (cannot be estimated from available data), including isolated reports.

Table 4 Adverse reactions reported in SPRINT Phase II Stratum 1

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE Grades)	Frequency of CTCAE Grade 3 and Above[†]
Eye disorders	Vision blurred	Common (8.0%)	-
Respiratory, thoracic & mediastinal disorders	Epistaxis	Very common (28.0%)	-
	Dyspnoea*	Common (4.0%)	-
Gastrointestinal disorders	Vomiting	Very common (82.0%)	Common (6.0%)
	Abdominal pain*	Very common (76.0%)	-
	Diarrhoea	Very common (70.0%)	Very common (16.0%)
	Nausea	Very common (66.0%)	Common (2.0%)
	Stomatitis	Very common (50.0%)	-
	Constipation	Very common (34.0%)	-
	Dry mouth	Common (4.0%)	-
Skin and subcutaneous tissue disorders	Rash (all)*	Very common (78.0%)	Common (6.0%)
	Dry skin	Very common (60.0%)	-
	Rash acneiform*	Very common (50.0%)	Common (4.0%)
	Paronychia	Very common (46.0%)	Common (6.0%)
	Pruritus	Very common (46.0%)	-
	Dermatitis*	Very common (36.0%)	Common (4.0%)
	Hair changes*	Very common (32.0%)	-
Musculoskeletal and connective tissue disorders	Musculoskeletal pain*	Very common (58.0%)	-
Nervous system disorders	Headache	Very common (48.0%)	Common (2.0%)
Renal and urinary system disorder	Haematuria	Very common (22.0%)	Common (2.0%)
	Proteinuria	Very common (22.0%)	-
Metabolism and nutrition disorder	Decreased appetite	Very common (22.0%)	-

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE Grades)	Frequency of CTCAE Grade 3 and Above†
Cardiac system disorder	Decreased ejection fraction	Very common (22.0%)	-
	Sinus tachycardia	Very common (20.0%)	-
Infections	Skin infection*	Very common (20.0%)	Common (2.0%)
General disorders	Asthenic events*	Very common (56.0%)	-
	Pyrexia	Very common (56.0%)	Common (8.0%)
	Peripheral oedema*	Very common (12.0%)	-
	Facial oedema*	Common (4.0%)	-
Investigations	Increased blood pressure*	Very common (18.0%)	-

Per National Cancer Institute CTCAE version 4.03
CPK = creatine phosphokinase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.
† All events were CTCAE grade 3, except for one CTCAE grade 4 event of blood CPK increased and one CTCAE grade 4 event of blood creatinine increased. There were no deaths.
*Adverse reactions based on grouping of individual Preferred Terms (PT):
Rash (all): Dermatitis acneiform, Rash maculo-papular, Rash papular, Rash, Rash erythematous, Rash macular
Rash (acneiform): Dermatitis acneiform
Hair changes: Alopecia, Hair colour change
Asthenic events: Fatigue, Asthenia
Peripheral oedema: Oedema peripheral, Oedema
Facial oedema: Periorbital oedema, Face oedema
Dyspnoea: Dyspnoea exertional, Dyspnoea, Dyspnoea at rest
Increased blood pressure: Hypertension, Blood pressure increased
Abdominal pain: Abdominal pain, Abdominal pain upper
Dermatitis: Dermatitis, Dermatitis atopic, Dermatitis diaper, Eczema, Seborrheic dermatitis, Skin irritation
Musculoskeletal pain: Pain in extremity, Back pain, Neck pain, Musculoskeletal pain
Skin infection: Skin infection, Abscess, Cellulitis, Impetigo, Staphylococcal skin infection

Table 5 presents the laboratory abnormalities in SPRINT Phase II Stratum 1.

Table 5 Select Laboratory Abnormalities (≥ 15%) Worsening from Baseline in Patients Who Received KOSELUGO in SPRINT Phase II Stratum 1

Laboratory Abnormality	KOSELUGO	
	All Grades (%)*	Grade ≥ 3 (%)
Chemistry		
Increased creatine phosphokinase (CPK)	79	7§
Decreased albumin	51	0
Increased aspartate aminotransferase (AST)	41	2
Increased alanine aminotransferase (ALT)	35	4
Increased lipase	32	5
Increased potassium	27	4
Decreased potassium	18	2§

Laboratory Abnormality	KOSELUGO	
	All Grades (%)*	Grade ≥ 3 (%)
Increased alkaline phosphatase	18	0
Increased amylase	18	0
Increased sodium	18	0
Decreased sodium	16	0
Blood creatinine increased	28	2
Hematology		
Decreased hemoglobin	41	4
Decreased neutrophils	33	4
Decreased lymphocytes	20	2

* The denominator used to calculate the rate varied from 39 to 49 based on the number of patients with a baseline value and at least one post-treatment value.
§ Includes one Grade 4 increased CPK and one Grade 4 increased potassium.

Adverse Reactions Identified in Other Clinical Trials

Table 6 presents the adverse reactions identified from other clinical trial experience in adult patients (N=347), with multiple tumour types, receiving treatment with KOSELUGO (75 mg twice daily):

Table 6 Adverse Reactions Reported in Adult Patients with multiple tumour types but not Reported in SPRINT Phase II Stratum I

MedDRA SOC	MedDRA Term	Overall Frequency (All CTCAE Grades)	Frequency of CTCAE Grade 3 and Above†
Eye disorders	Retinal Pigment Epithelial Detachment (RPED)/Central Serous Retinopathy (CSR)*	Uncommon (0.6%)	-
	Retinal Vein Occlusion (RVO)*	Uncommon (0.3%)	-

* Adverse reactions based on grouping of individual Preferred Terms (PT):
CSR/RPED: Detachment of macular retinal pigment epithelium, Chorioretinopathy
RVO: Retinal vein occlusion, Retinal vein thrombosis, Retinal vascular disorder

In addition, a single event of RPED was reported in a paediatric patient receiving KOSELUGO monotherapy (25 mg/m^2 twice daily) for pilocytic astrocytoma involving the optic pathway in an externally sponsored paediatric study, see Section 4.2 and 4.4.

Description of selected adverse reactions

LVEF reduction

In SPRINT, LVEF reduction (PT: ejection fraction decreased) was reported in 11 (22%) patients; all cases were grade 2, asymptomatic and did not lead to dose interruptions, reductions, or discontinuation. Of the 11 patients, 6 patients recovered and for 5 patients the outcome was not reported. The median time to first occurrence of LVEF reduction was 226 days (median duration 78 days). The majority of LVEF reduction adverse events were reported as reductions from baseline (≥10% reduction) but were considered to remain in the normal range. Patients with LVEF lower than the institutional LLN at baseline were not included in the pivotal study.

Decrease in LVEF should be managed using treatment interruption, dose reduction or treatment discontinuation (see Sections 4.2 and 4.4).

Blurred vision

In SPRINT, grade 1 and 2 events of blurred vision were reported in 4 (8%) patients. Two patients required dose interruption. All events were managed without dose reduction. No retinal involvement was observed in the ophthalmic examinations of paediatric patients.

If patients report new visual disturbances a complete ophthalmological assessment is recommended. Retinal toxicities can be managed using treatment interruption, dose reduction or treatment discontinuation (see Sections 4.2 and 4.4).

Paronychia

In SPRINT, paronychia was reported in 23 (46%) patients, the median time to first onset of maximum grade paronychia adverse event was 306 days and the median duration of events was 96 days. The majority of these events were grade 1 or 2 and were treated with supportive or symptomatic therapy and dose modification. Grade ≥3 events occurred in three (6%) patients. Seven patients had a KOSELUGO dose interruption for adverse events paronychia, of whom 3 had dose interruption followed by dose reduction (2 patients required a second dose reduction). In one patient (2%), the event led to discontinuation.

Blood creatine phosphokinase (CPK) increase

Adverse events of blood CPK elevation occurred in 76% of patients in SPRINT. The median time to first onset of the maximum grade CPK increase was 106 days and the median duration of events was 126 days. The majority of events were grade 1 or 2 and resolved with no change in KOSELUGO dose. Grade ≥3 events occurred in three (6%) patients. A grade 4 event led to treatment interruption followed by dose reduction.

Gastrointestinal toxicities

Vomiting (82%), abdominal pain (76%), diarrhoea (70%), nausea (66%), stomatitis (50%), and constipation (34%) were the most commonly reported gastrointestinal (GI) reactions. The majority of these cases were grade 1 or 2 and did not require any dose interruptions or dose reductions.

Grade 3 events were reported for diarrhoea (16%), nausea (2%), and vomiting (6%). For one patient diarrhoea led to dose reduction and subsequent discontinuation. No dose reduction or discontinuation was required for adverse events of nausea, vomiting or stomatitis. No grade ≥4 events were reported.

Skin toxicities

In SPRINT, acneiform rash was observed in 25 (50%) patients (median time to onset 13 days; median duration of 60 days for the maximum CTCAE grade event). The majority of these cases were grade 1 or 2, observed in post-pubertal patients (>12 years) and did not require any dose interruptions or reductions. Grade 3 events were reported for 4%.

Other (non-acneiform) rashes were observed in 35 (70%) patients in the pivotal study and were predominantly grade 1 or 2.

Hair changes

In SPRINT, 32% of patients experienced hair changes (reported as hair lightening [PT: hair colour changes] in 11 patients (22%) and hair thinning [PT: alopecia]) 12 patients (24%); in 7 patients (14%) both alopecia and hair colour changes were reported during treatment. All cases were grade 1 and did not require dose interruption or dose reduction.

4.9 Overdose

There is no specific treatment for overdose. If overdose occurs, patients should be treated supportively with appropriate monitoring as necessary. Dialysis is ineffective in the treatment of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Selumetinib is an orally available, potent and selective inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) that is not competitive with respect to ATP. MEK1/2 proteins are critical components of the *RAS*-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. Selumetinib blocks MEK activity and inhibits growth of RAF-MEK-ERK pathway activated cell lines. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated.

Pharmacodynamic effects

In genetically modified mouse models of NF1 that generate neurofibromas that recapitulate the genotype and phenotype of human type 1 neurofibromas, oral dosing of selumetinib inhibits ERK phosphorylation, reduces neurofibroma volume, proliferation, number and growth.

Cardiac electrophysiology

The effect of selumetinib on the QTc interval following a single 75 mg oral dose, in a placebo- and positive-controlled (moxifloxacin) study, in 48 healthy adults showed no clinically relevant effect on the QTc interval (<10 msec change). A pharmacokinetic-pharmacodynamic analysis predicted a <10 msec change at 150 mg dose (3 times higher than the recommended maximum dose of 50 mg in paediatric patients with NF1).

Clinical efficacy

SPRINT

The efficacy of KOSELUGO was evaluated in an open-label, multi-centre, single-arm study [SPRINT Phase II Stratum 1 (NCT01362803)] of 50 paediatric patients with NF1 inoperable PN that caused significant morbidity. Morbidities that were present in ≥20% of patients included disfigurement, motor dysfunction, pain, airway dysfunction, visual impairment, and bladder/bowel dysfunction. Inoperable PN was defined as a PN that could not be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN. Patients received 25 mg/m^2 (BSA) twice daily, for 28 days (1 treatment cycle), on a continuous dosing schedule. Treatment was discontinued if a patient was no longer deriving clinical benefit, experienced unacceptable toxicity or PN progression, or at the discretion of the investigator.

The target PN, the PN that caused relevant clinical symptoms or complications (PN-related morbidities), was evaluated for response rate using centrally read volumetric magnetic resonance imaging (MRI) analysis per Response Evaluation in Neurofibromatosis and

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

Patients had target PN MRI volumetric evaluations and clinical outcome assessments, which included functional assessments and patient reported outcomes.

The median age of the patients was 10.2 years (range: 3.5 - 17.4 years), 60% were male, 84% were Caucasian.

Disease characteristics at baseline are provided in Table 7.

Table 7 Baseline disease characteristics

Characteristics	SPRINT (N = 50)
Target PN volume (mL):	
Median (range)	487.5 (5.6 - 3820)
Number of PN related morbidities:	
Median (range)	3 (1 - 4)
Target PN related morbidities (%):	
Disfigurement	88%
Motor dysfunction	66%
Pain	52%
Airway dysfunction	32%
Visual impairment	20%
Bladder/bowel dysfunction	20%

The primary efficacy endpoint was Objective Response Rate (ORR), defined as the percentage of patients with complete response (defined as disappearance of the target PN) or confirmed partial response (defined as ≥20% reduction in PN volume, confirmed at a subsequent tumour assessment within 3-6 months), based on NCI centralised review. Duration of Response (DoR) was also evaluated.

The primary endpoint, ORR was 66% (95% CI 51.2 – 78.8). An independent centralized review of tumour response per REiNS criteria resulted in an ORR of 44% (95% CI 30, 59). Time to onset of response for the majority of patients (24/33 [72.7%]) was within 8 cycles (range 4 – 20 cycles).

The median DoR from onset of response was not reached; at the time of data cut-off the median follow-up time was 24 cycles. Of the 33 patients who had confirmed partial responses, 29 (87.9%) remained in response after 12 cycles; 4 patients were censored not due to progression. The probability to remain in response after 12 and 16 cycles, estimated using the Kaplan-Meier method, was 100% (95% CI not estimated) and 96.2% (95% CI 75.7 – 99.4), respectively. The median time from treatment initiation to disease progression while on treatment was not reached.

Table 8 NF1 PN efficacy results from SPRINT

Efficacy Parameter	SPRINT (N = 50)
Objective Response Rate [a]	
Objective Response Rate, % (95% CI)	66.0 (51.2 – 78.8)
Best objective response, n (%) [b, c]	
Complete Response	0
Confirmed Partial Response	33 (66%)
Unconfirmed Partial Response	4 (8%)
Stable Disease	11 (22%)
Progressive Disease	0
Duration of Response [d]	
Median (95% CI) months	NR (NE – NE)
Estimated percentage remaining in response	
≥12 cycles, % (95% CI)	100 (NE – NE)
≥16 cycles, % (95% CI)	96 (75.7 – 99.4)

CI - confidence interval, NE – not estimated, NR - not reached

[a] Responses required confirmation at least 3 months after the criteria for first partial response were met.

[b] Complete response: disappearance of the target lesion; Partial Response: decrease in target PN volume by ≥20% compared to baseline; Stable Disease: insufficient volume change from baseline to qualify for either partial response or progressive disease; Progressive Disease: increase in target PN volume by ≥20% compared to baseline or the documented time of best response.

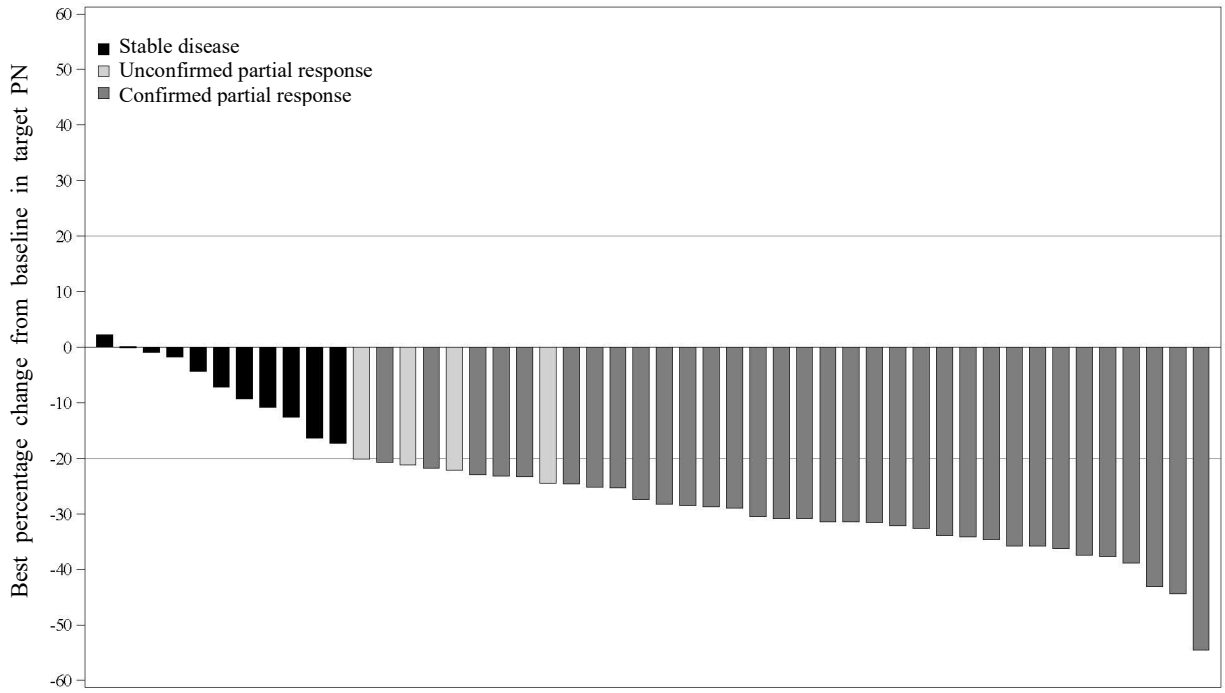
[c] Two patients were not evaluable.

[d] Duration of Response from onset of response based on Kaplan-Meier analysis in patients with confirmed partial response.

At the time of data cut-off, 28 (56%) patients remained in confirmed partial response, 2 (4%) had unconfirmed partial responses, 15 (30%) had stable disease and 3 (6%) had progressive disease.

The median best percentage change in PN volume from baseline was -27.85% (range: 2.2% to -54.5%). Figure 1 shows the best percentage change in target PN volume for each patient.

Figure 1 Waterfall plot of best percentage change from baseline in target PN volume[a]



[a] Best percentage change in target PN volume is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. Two patients were not evaluable.

Clinical Outcome Assessments

Pain intensity of the target PN was self-reported by patients ≥8 years of age using an 11-point Numeric Rating Scale (NRS-11). A clinically meaningful reduction in pain (defined as, ≥2-point decrease from baseline) was reported for 50% of patients (n=12) at pre-Cycle 13; 12 patients (50%) reported no change (10 of which had a baseline score of ≤1) and no patients showed deterioration.

Parent-reported (all patients) and patient-reported (≥8 years of age) health-related quality of life (HRQoL) was assessed using the Peds-QL questionnaire. Based on MMRM analysis, improvement in HRQoL was reported by patients and parents at pre-Cycle 13 with a mean change from baseline of 6.68 (95% CI 1.34 – 12.02) and 12.7 (95% CI 8.91 – 16.55) respectively. These results should be interpreted in the context of the open-label, single-arm study design and therefore taken cautiously.

5.2 Pharmacokinetic properties

At the recommended dosage of 25 mg/m^2 twice daily in paediatric patients (3 to ≤18 years old), the geometric mean (coefficient of variation [CV%]) C_{max} following the first dose and at steady state was 731 (62%) ng/mL and 798 (52%) ng/mL, respectively. The mean area under the plasma drug concentration curve ($AUC_{0\text{-}12h}$) following the first dose was 2009 (35%) ng·h/mL and the $AUC_{0\text{-}6h}$ at steady state was 1958 (41%) ng·h/mL. Selumetinib AUC and C_{max} increases proportionally over a dose range from 20 mg/m^2 to 30 mg/m^2 (0.8 to 1.2 times the recommended dose). Minimal accumulation of ~1.1 fold was observed at steady state upon twice daily dosing.

In paediatric patients, at a dose level of 25 mg/m^2, selumetinib has an apparent oral clearance of 8.8 L/h, mean apparent volume of distribution at steady state of 78 L and mean elimination half-life of ~6.2 hours.

Absorption

In healthy adult subjects, the mean absolute oral bioavailability of selumetinib was 62%. Following oral dosing, selumetinib is rapidly absorbed, producing peak steady state plasma concentrations (T_{max}) between 1-1.5 hours post-dose.

Effect of food

In separate clinical studies, in healthy adult subjects and in adult patients with advanced solid malignancies at a dose of 75 mg, co-administration of selumetinib with a high-fat meal resulted in a mean decrease in C_{max} of 50% and 62%, respectively, compared to fasting administration. Selumetinib mean AUC was reduced by 16% and 19%, respectively, and the time to reach maximum concentration (T_{max}) was delayed by approximately 1.5 hours (see Section 4.2).

In healthy adult subjects at a dose of 50 mg, co-administration of selumetinib with a low-fat meal resulted in 60% lower C_{max} when compared to fasting administration. Selumetinib AUC was reduced by 38%, and T_{max} was delayed by approximately 0.9 hours (see Section 4.2).

Effect of gastric acid reducing agents on KOSELUGO

KOSELUGO capsules do not exhibit pH dependent dissolution. KOSELUGO can be used concomitantly with gastric pH modifying agents (i.e. H_2-receptor antagonists and proton pump inhibitors) without any restrictions.

Distribution

The mean apparent volume of distribution at steady state of selumetinib across 20 to 30 mg/m^2 ranged from 78 to 171 L in paediatric patients, indicating moderate distribution into tissue.

In vitro plasma protein binding is 98.4% in humans. Selumetinib mostly binds to serum albumin (96.1%) than α-1 acid glycoprotein (<35%).

Biotransformation/ Metabolism

In vitro, selumetinib undergoes Phase 1 metabolic reactions including oxidation of the side chain, N-demethylation, and loss of the side chain to form amide and acid metabolites. CYP3A4 is the predominant isoform responsible for selumetinib oxidative metabolism with CYP2C19, CYP1A2, CYP2C9, CYP2E1 and CYP3A5 involved to a lesser extent. *In vitro* studies indicate that selumetinib also undergoes direct Phase 2 metabolic reactions to form glucuronide conjugates principally involving the enzymes UGT1A1 and UGT1A3. Glucuronidation is a significant route of elimination for selumetinib Phase 1 metabolites involving several UGT isoforms.

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

Elimination

In healthy adult volunteers, following a single oral 75 mg dose of radiolabelled selumetinib, 59% of the dose was recovered in faeces (19% unchanged) while 33% of the administered dose (<1% as parent) was found in urine by 9 days of sample collection.

Interactions

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

Interactions with transport proteins

Based on *in vitro* studies, selumetinib is a substrate for BCRP and P-gp transporters but is unlikely to be subjected to clinically relevant drug interactions at the recommended paediatric dose. *In vitro* studies suggest that selumetinib does not inhibit the breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, MATE1 and MATE2K at the recommended paediatric dose. A clinically relevant effect on the pharmacokinetics of concomitantly administered substrates of OAT3 cannot be excluded.

Special populations

Renal impairment

The exposure of 50 mg oral selumetinib was investigated in adult subjects with normal renal function (n=11) and subjects with ESRD (n=12). The ESRD group showed 16% and 28% lower C_{max} and AUC, respectively, with the fraction of unbound selumetinib being 35% higher in ESRD subjects. As a result, the unbound C_{max} and AUC ratios were 0.97 and 1.13 in the ESRD group when compared to the group with normal renal function. A small increase, approximately 20% AUC, in the N-desmethyl metabolite to parent ratio was detected in the ESRD group when compared to the normal group. As exposure in ESRD subjects was similar to those with normal renal function, investigations in mild, moderate and severe renally impaired subjects were not performed. Renal impairment is expected to have no meaningful influence on the exposure of selumetinib (see Section 4.2).

Hepatic impairment

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

Ethnicity

Following a single-dose, selumetinib exposure appears to be higher in Japanese, non-Japanese-Asian and Indian healthy adult volunteers compared to Western adult volunteers. However, there is considerable overlap with Western subjects when corrected for body weight or BSA (see Section 4.2).

Adult patients (>18 years old)

The PK parameters in adult healthy volunteers and adult patients with advanced solid malignancies, are similar to those in paediatric patients (3 to ≤18 years old) with NF1.

In adult patients with solid malignancies, at a dose of 75 mg twice daily, C_{max} and geometric mean (%CV) AUC were 1307 (76%) ng/mL and 4736 (37%) ng·h/mL, respectively. Peak plasma concentrations of selumetinib were achieved 1.5-hour post-dose with a mean elimination half-life of 7.8 hours. C_{max} and AUC increased dose proportionally over a 25 mg to 100 mg dose range, and administration of 75 mg selumetinib twice daily resulted in minimal accumulation of ~1.2 fold.

5.3 Preclinical safety data

Mutagenicity

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 (NOEL) was approximately 27-times greater than clinical free exposure at the maximum recommended human dose (MRHD) of 25 mg/m^2.

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 free clinical AUC at MRHD 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 MRHD.

Repeat-dose toxicity

In repeat-dose toxicity studies in mice and rats, the main effects seen after selumetinib exposure were in the skin, scabs associated with microscopic erosions and ulceration in rats at a free exposure similar to the clinical exposure (free AUC) at the MRHD; inflammatory and ulcerative GI tract findings in mice associated with secondary changes in the liver and lymphoreticular system at free exposures approximately 28 times the clinical free exposure at the MRHD; and growth plate (physeal) dysplasia in male rats at a free exposure 11 times the clinical free exposure at the MRHD. GI findings showed evidence of reversibility following a recovery period. Reversibility for skin toxicities and physeal dysplasia were not evaluated.

Reproductive toxicology

Fertility

In a 6-month mouse study, selumetinib did not affect male mating performance at any dose up to 20 mg/kg twice daily corresponding to approximately 22-times the human clinical exposure based on free AUC at the MRHD. In female mice exposed to selumetinib at 12.5 mg/kg twice daily, mating performance and fertility were not affected, but the number of live foetuses was slightly reduced. Following a three-week treatment withdrawal period, no effects were apparent on any parameter. The no observed adverse effect level (NOAEL) for both maternal toxicity and effects on reproductive performance was 2.5 mg/kg twice daily (approximately, 3.5-fold human free exposure at the MRHD).

Embryofoetal toxicity

In embryofoetal 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 an exposure >3.5-fold the clinical exposure at MRHD based on free AUC and indicate that selumetinib may have potential to cause defects in 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. The incidence of malformations (prematurely open eye(s) and cleft palate) was increased at all dose levels. Malformations occurred at maternal concentration (C_{max}) 0.4-fold below the mean free clinical concentration at MRHD.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The names of excipients may vary according to region.

10 mg hard capsule

- Capsule content: Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol 1000 succinate).

- Capsule shell: Hypromellose (E 464), Carrageenan, Potassium chloride, Titanium dioxide (E 171), Carnauba wax and Purified water.

- Printing ink: Shellac glaze, Iron oxide black, Propylene glycol, Ammonium hydroxide 28%.

25 mg hard capsule

- Capsule content: Vitamin E polyethylene glycol succinate (D α-tocopheryl polyethylene glycol 1000 succinate).

- Capsule shell: Hypromellose (E 464), Carrageenan, Potassium chloride, Titanium dioxide (E 171), FD&C Blue 2 (E 132), Ferric oxide yellow (E 172), Purified water, Carnauba wax and/or Corn starch.

- Printing ink: Ferric oxide red, Ferric oxide yellow, FD&C blue 2 aluminium lake, Carnauba wax, White shellac, Glyceryl monooleate.

6.2 Incompatibilities

None.

6.3 Shelf life

Please refer to expiry date on outer carton.

6.4 Special precautions for storage

Do not store above 30°C.

Store in the original bottle to protect from moisture and light.

Do not remove desiccant.

6.5 Nature and contents of container

10 mg hard capsule: HDPE plastic bottle with a white child-resistant closure made of PP. The HDPE bottle contains silica gel desiccant and 60 hard capsules.

25 mg hard capsule: HDPE plastic bottle with a blue child-resistant closure made of PP. The HDPE bottle contains silica gel desiccant and 60 hard capsules.

6.6 Instructions for use, handling and disposal

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

Product owner

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