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RESEARCH**

APPLICATION NUMBER:

213756Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number	213756
Priority or Standard	Priority
Submit Date	9-13-2019
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PDUFA Goal Date	5-13-2020
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Division/Office	OOD/DO2
Review Completion Date	4-3-2020
Established Name	Selumetinib
(Proposed) Trade Name	Koselugo
Pharmacologic Class	Kinase inhibitor
Code name	AZD6244
Applicant	AstraZeneca Pharmaceuticals LP
Formulation	Capsules
Dosing Regimen	25 mg/m ² orally twice daily, every 12 hours
Applicant Proposed Indication	Treatment of pediatric patients, aged 3 years and above, with neurofibromatosis-1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN).
Recommendation on Regulatory Action	Approval
Recommended Indication	Treatment of pediatric patients 2 years of age and older with neurofibromatosis-1 (NF1) who have symptomatic, inoperable plexiform neurofibroma (PN).

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
A/G	albumin:globulin
AHI	Apnoea-Hypopnoea Index
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the plasma concentration-time curve
AUC ₍₀₋₁₂₎	area under the plasma concentration-time curve from time 0 to 12 hours
AUC ₍₀₋₂₄₎	area under the plasma concentration-time curve from time 0 to 24 hours
BID	twice daily
BiPAP	bilevel positive airway pressure
BLQ	below limit for quantitation
BMD	bone mineral density
BP	blood pressure
BRA	Benefit Risk Assessment
BSA	body surface area
BTD	Breakthrough Therapy Designation
BUN	blood urea nitrogen
C3D	Cancer Central Clinical Database
ca.	circa; approximately
CAEPR	Comprehensive Adverse Event and Potential Risks
CBC	complete blood count
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
ClinRo	clinician reported outcome
C _{max}	maximum observed plasma concentration
CMT	clinically meaningful threshold
CNS	central nervous system
COA	Clinical Outcome Assessment

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CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CSP	clinical study protocol
csr	central serous retinopathy
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Programme
CV%	coefficient of variation
CYP	cytochrome P450
DAE	AEs resulting in permanent discontinuation of selumetinib
DCO	data cut-off
DDI	drug-drug interaction
DEXA	dual-energy X-ray absorptiometry
DILI	drug induced liver injury
DLT	dose limiting toxicity
DMF	Drug Master File
DoR	duration of response
DVQ	dysfunctional voiding questionnaire
EAP	Early Access Program
ECG	electrocardiogram
ECHO	echocardiogram
EFD	embryofetal development
EMA	European Medicines Agency
EMH	extramedullary hematopoiesis
ERK	extracellular signal related kinase
ESR	externally-sponsored scientific research
ESRD	end stage renal disease
F	female
FAS	full analysis set
FDA	Food and Drug Administration
FEV ₁	forced expiratory volume in 1 second
FEV _{0.75}	forced expiratory volume in 0.75 seconds
GCP	Good Clinical Practice
GD	Gestation Day
GGT	gamma glutamyltransferase
GI	Gastrointestinal
GIC	Global Impression of Change
GLP	Good Laboratory Practice
HCP	health care provider
HD	high dose

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hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HRQoL	health related quality of life
hyd-sulfate	hydrogen sulfate
ICC	intraclass correlation coefficient
ICH	International Conference on Harmonisation
ICR	independent central review
IND	Investigational New Drug
IOP	intraocular pressure
IP	intraperitoneal
IPR	individual patient review
IRB	Institutional Review Board
ISS	integrated summary of safety
LD	low dose
LLN	lower limit of normal
LVEF	left ventricular ejection fraction
6MWT	6-minute walk test
M	male
Max	maximum
MD	mid dose
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MIE	micronucleated immature erythrocytes
Min	minimum
MMRM	mixed model repeated measures
MMT	manual muscle test
MPNST	malignant peripheral nerve sheath tumor
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N	nodular PN
NC	not calculated
NCI	National Cancer Institute
NDA	new drug application
NE	not evaluable
NIH	National Institute of Health
NF1	neurofibromatosis type 1
NME	new molecular entity
NMU	N-nitrosemethylurea
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NRS-11	numeric rating scale-11
NSCLC	non-small cell lung cancer

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OAE	other significant adverse event
ObsRo	observer reported outcome
ODD	Orphan Drug Designation
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cells
PBPK	physiologically-based PK
PCE	polychromatic erythrocytes
PedsQL	Pediatric Quality of Life Inventory
PerfO	performance outcome
PFS	progression-free survival
PFT	pulmonary function test
P-gp	P-glycoprotein
PI	principle investigator
PII	pain interference index
PK	pharmacokinetics
PN	plexiform neurofibroma
PND	postnatal day
PPND	pre and postnatal development
POB	Pediatric Oncology Branch
PPI	proton pump inhibitors
PR	partial response
PRO	patient-reported outcome
PROMIS	patient-reported outcomes measurement information system
PT	preferred term
q21d	every 21 days
QD	once daily
QOL	quality of life
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's correction formula
RDI	relative dose intensity
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
REMS	risk evaluation and mitigation strategy
RMQ	Responsibility for Medication Questionnaire
ROM	range of motion
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation

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SN	solitary nodular PN
SOC	system organ class
SPEER	Specific Protocol Exceptions to Expedited Reporting
SUSAR	suspected unexpected serious adverse reaction
TK	toxicokinetic(s)
t_{max}	time to maximum observed plasma concentration
TTP	time to progression
TTR	time to response
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
U	unconfirmed response
US(A)	United States (of America)
UV	ultraviolet
V _{ss}	geometric mean volume of distribution

1 Executive Summary

1.1. Product Introduction

Selumetinib (AZD6244) is an orally bioavailable, non-ATP competitive kinase inhibitor that targets mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinases 1 and 2 (MEK1/2); the established pharmacological class is kinase inhibitor. MEK1/2 are ubiquitously expressed proteins that are part of the Ras-Raf-MAPK-ERK signaling transduction cascade. Activation of the Ras-MAPK signaling pathway leads to cell proliferation and is involved in a large number of various types of cancer.

Neurofibromatosis type I (NF1) is a syndrome caused by germline mutations in the *NF1* gene resulting in widespread phenotypic outcomes, including plexiform neurofibromas (PN). *NF1* codes for the protein neurofibromin, a widely expressed Ras GTPase activating protein (GAP), that limits downstream Ras signaling. Mutations in *NF1* commonly lead to increased Ras pathway signaling and dysregulated growth. Blocking downstream Ras signaling by targeting MEK1/2 may help slow or reduce plexiform neurofibroma growth.

PNs are nerve sheath tumors that typically grow along large nerves and plexuses and are present at birth. PNs may develop along nerves anywhere in the body, and may be located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion [ROM]), pain, respiratory impairment, visual dysfunction, and neurological dysfunction.

Selumetinib is a new molecular entity that is not approved currently by the United States Food and Drug Administration (The FDA). The drug was granted Orphan Product Designation for the treatment of NF1 in February 2018, and Breakthrough Therapy Designation was granted in March 2019.

The Applicant has proposed the following indication for selumetinib:

For the treatment of pediatric patients, aged 3 years and above, with neurofibromatosis-1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The current New Drug Application (NDA) for selumetinib was submitted pursuant to Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 Code of Federal Regulations (CFR)

314.126(a)(b). Review teams from all disciplines have recommended that regular approval be granted for selumetinib for the following indication:

For the treatment of pediatric patients 2 years of age and older with neurofibromatosis-1 (NF1) who have symptomatic, inoperable plexiform neurofibroma (PN).

The benefit: risk assessment for selumetinib favors the benefit of the drug for the recommended indicated population. The drug has demonstrated a statistically significant, robust, and clinically meaningful effect on ORR that is durable and associated with improvements in disease-related morbidities. These factors represent direct clinical benefit to patients and warrant regular approval of the drug. Additionally, the safety profile for the drug is consistent with other MEK inhibitors and appears acceptable to patients taking the drug who have a serious and life-threatening disease.

The recommended dosing regimen of selumetinib is 25 mg/m² orally twice daily without food two hours before and one hour after each dose administered continuously until disease progression or intolerable toxicity; for a minimum BSA of 0.55 m² the recommended dose is 20 mg in the morning and 10 mg in the evening and the recommended dose is capped at 50 mg when the BSA is ≥1.9 m². A postmarketing requirement is included as part of the action on this application. Required is the submission of data from a pharmacokinetic trial in pediatric patients to confirm the effect of a low-fat meal on selumetinib exposure with the marketed capsule formulation and evaluate whether administration of selumetinib with food may alleviate gastrointestinal toxicities, and in order to confirm appropriate dosing with a low-fat meal that maintains efficacy with acceptable safety.

The recommendation to approve selumetinib is based on results from a single trial, entitled, “A Phase I/II Study of the Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor Selumetinib (AZD6244; HYD Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)” (SPRINT), specifically from Phase II, Stratum 1 of the trial. SPRINT was an open-label, single arm, multi-center trial conducted by the National Cancer Institute (NCI) Pediatric Oncology Branch (POB). Fifty pediatric patients with NF1 and PN-related morbidity were enrolled. The major efficacy outcome measure for the trial was overall response rate (ORR), or 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 tumor assessment within 3-6 months). The results from SPRINT Phase II Stratum 1 demonstrated an overall response rate (ORR) per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria of 66% (95% CI: 51, 79) based upon NCI central review, and 44% (95% CI: 30, 59) based upon independent central review (ICR). Among the 33 responding patients included in the NCI assessment, the median duration of response (DOR) was not reached while 82% of patients had a DOR of at least 12 months. Supportive data for the application were derived from the observed ORRs in SPRINT Phase 1 [67% (95% CI: 45, 84)] and SPRINT Phase II Stratum 2 [68% (95% CI: 47, 85)], which were

consistent with the Phase II Stratum 1 results in rate and durability. Additionally, a natural history study of NF1 conducted by the NCI POB was submitted with the application to provide external control data; however, no formal statistical comparisons were made by the FDA. The study did, nevertheless, demonstrate that a key characteristic of NF1 PN is the uncommon occurrence of spontaneous regression such that the observed tumor responses in SPRINT are concluded to be the effect of the drug.

Given the benign, albeit morbid, nature of NF1 PN, clinical outcomes data were also submitted with the application and considered a critical element of the trial to demonstrate the clinical relevance of treatment when associated with the observed radiographic response results. The SPRINT trial evaluated selumetinib effects on PN-related functional impairment, symptoms, and disfigurement using various clinical outcomes assessment (COA) tools and measures as well as photographic evaluations conducted as part of scheduled tumor response assessments. Despite the limitations of the single arm trial design and the relatively small sample sizes available for analysis of specific morbidities, a general trend toward an association between a reduction in tumor volume and durable improvement in clinical outcomes was observed.

The primary safety risks of selumetinib are consistent with the profiles of other approved MEK inhibitors. Adverse Drug Reactions (ADRs) in pediatric patients receiving selumetinib were frequent and varied. Serious adverse events occurred in 24% of patients; those occurring in two or more patients were anemia, hypoxia and diarrhea. Permanent discontinuation resulting from adverse events occurred in 12% of patients, and included increased creatinine, weight increase, diarrhea, paronychia, malignant peripheral nerve sheath tumor (MPNST), acute kidney injury, and skin ulcer. Dose interruptions as a result of adverse reactions occurred in 80% of patients while dose reductions after adverse events occurred in 24% of patients, and those occurring in more than 5% of patients included vomiting, paronychia, diarrhea, nausea, abdominal pain, rash, skin infection, influenza-like illness, pyrexia and weight gain. The most common adverse reactions observed in $\geq 40\%$ of patients were: vomiting, abdominal pain, rash, blood creatine phosphokinase increased, diarrhea, nausea, dry skin, asthenic events, fatigue, musculoskeletal pain, pyrexia, acneiform rash, hypoalbuminemia, and stomatitis.

A risk evaluation and mitigation strategy (REMS) is not recommended for selumetinib given the current safety profile and the experience of the medical community in managing expected MEK inhibitor toxicities. Given the intended chronic use of the drug for pediatric patients with NF-1 PN, postmarketing requirements and enhanced pharmacovigilance are included as part of the approval for this NDA. Long-term monitoring of patients will include evaluations for safety, growth and development. Risk management based on labeling as well as routine and enhanced pharmacovigilance will be employed to ensure the safe and effective use of selumetinib in the indicated population.

For the specifics of each discipline's decision on this application, please see the relevant sections of this review, or the separate review filed for that discipline.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Fifty pediatric patients with NF1 and PN-related morbidity were enrolled in Stratum 1 of SPRINT. The results from SPRINT Phase II Stratum 1 demonstrated an overall response rate (ORR) per REiNS criteria of 66% (95% CI: 51, 79) based upon NCI central review, and 44% (95% CI: 30, 59) based upon independent central review (ICR). Among the 33 responding patients included in the NCI assessment, the median duration of response (DOR) was not reached while 82% of patients had a DOR of at least 12 months. Supportive data for these findings came from the observed ORRs in SPRINT Phase 1 [67% (95% CI: 45, 84)] and SPRINT Phase II Stratum 2 [68% (95% CI: 47, 85)], which were consistent with the Phase II Stratum 1 results and similarly durable. Additionally, a natural history study of NF1 conducted by the NCI POB and submitted as with the application demonstrated that a key characteristic of NF1 PN is the uncommon occurrence of spontaneous regression such that the observed tumor responses in SPRINT is concluded to be the effect of the drug. The natural history study was submitted to provide external control data; however, no formal statistical comparisons were made.

Clinical outcomes data was also considered a critical element of the trial to demonstrate the clinical relevance of treatment. The SPRINT trial evaluated selumetinib effects on PN-related functional impairment, symptoms, and disfigurement using various COA tools and measures as well as photographic evaluations conducted as part of scheduled tumor response assessments. A general trend toward an association between reduction in tumor volume and durable improvement in clinical outcomes was observed.

The safety population evaluated for selumetinib consisted of a pooled population of 74 pediatric patients who received a dose ranging from 20 mg/m² to 30 mg/m² orally twice daily in SPRINT. Among these patients, 74% were exposed for greater than 2 years, and 23% were exposed for greater than 4 years. The safety population also included additional data from 347 adult patients who received selumetinib administered at various doses across a range of tumors in other clinical trials.

For the patient population with NF1 with inoperable PN, the safety assessment population also consisted of the fifty pediatric patients enrolled in SPRINT Phase II Stratum 1. Eligible patients were 2-18 years of age with NF1 and inoperable PN that was causing significant morbidity. Patients were excluded for abnormal LVEF, uncontrolled hypertension (blood pressure $\geq$ the 95th percentile for age, height, and sex), any current or past history of RVO or CSR, intraocular pressure > 21 mmHg (or upper limit of normal adjusted by age), uncontrolled glaucoma, and

inability to swallow whole capsules. Patients received selumetinib 25 mg/m² orally twice daily (n=50). Among these patients, 66% were exposed to the drug for greater than 2 years.

Serious adverse events occurred in 24% of patients; those occurring in two or more patients were anemia, hypoxia and diarrhea. Permanent discontinuation resulting from adverse events occurred in 12% of patients, and included increased creatinine, weight increase, diarrhea, paronychia, malignant peripheral nerve sheath tumor (MPNST), acute kidney injury, and skin ulcer. Dose interruptions as a result of adverse reactions occurred in 80% of patients while dose reductions after adverse events occurred in 24% of patients, and those occurring in more than 5% of patients included vomiting, paronychia, diarrhea, nausea, abdominal pain, rash, skin infection, influenza-like illness, pyrexia and weight gain. The most common adverse reactions observed in ≥ 40% of patients were: vomiting, abdominal pain, rash, blood creatine phosphokinase increased, diarrhea, nausea, dry skin, asthenic events, fatigue, musculoskeletal pain, pyrexia, acneiform rash, hypoalbuminemia, and stomatitis.

The data observed for the durable overall response rates in SPRINT Phase II Stratum 1 were statistically significant, robust, and clinically meaningful. These results were associated with the COAs assessed during the trial and there was a positive trend observed between tumor shrinkage and the COAs. The safety profile of the drug is consistent with the known safety profile of MEK inhibitors, and the drug has been appropriately labelled for both class effects of the drug and adverse reactions observed in the pediatric population. The benefit: risk assessment for selumetinib is favorable for the treatment of pediatric patients 2 years of age and older with NF1 and symptomatic, inoperable PN a non-malignant disease that causes severe morbidity, is serious, and life threatening.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	NF1 is a progressive multi-system disease characterized by progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and the associated morbidities can be severe. Loss of NF1 function favors the GTP-bound active form of RAS, resulting in activation of the RAF/MEK/ERK pathway, which can be the cause of or sustain the growth of various tumor types, such as benign or malignant tumors. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system. PNs are one of the most common benign tumors, which occur in approximately 20% to 50% of NF1 patients	NF1 is a rare, progressive, and highly morbid condition that can lead to fatal outcomes depending upon the location of the tumor. It is a serious and life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	PNs are nerve sheath tumors that typically grow along large nerves and plexuses and are present at birth. PNs may develop along nerves anywhere in the body, and may be located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, respiratory impairment, visual dysfunction, and neurological dysfunction.	
<u>Current Treatment Options</u>	None	Safe and effective treatments for this highly morbid condition are needed.
<u>Benefit</u>	- The results from SPRINT Phase II Stratum 1 demonstrated a statistically significant, robust, and clinically meaningful overall response rate (ORR) per REiNS criteria of 66% (95% CI: 51, 79) based upon NCI central review. and 44% (95% CI: 30, 59) based upon independent central review (ICR). Discordance between the NCI and IRC assessments of response is attributable to the small number of patients and five responders who had responses greater than 19%, just below the cutoff of 20% which defined a partial response in the trial. - Among the 33 responding patients included in the NCI assessment, the median duration of response (DOR) was not reached while 82% of patients had a DOR of at least 12 months. Supportive data for these findings came from the observed ORRs in SPRINT Phase 1 [67% (95% CI: 45, 84)] and SPRINT Phase II Stratum 2 [68% (95% CI: 47, 85)], which were consistent with the Phase II Stratum 1 results and similarly durable.	Substantial evidence of effectiveness was demonstrated for selumetinib in the patient population being indicated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Additionally, a natural history study of NF1 conducted by the NCI POB and submitted as with the application demonstrated that a key characteristic of NF1 PN is the uncommon occurrence of spontaneous regression such that the observed tumor responses in SPRINT can be concluded to be the effect of the drug. The natural history study was submitted to provide external control data; however, no formal statistical comparisons were made.	
<u>Risk and Risk Management</u>	• The pooled safety population evaluated for selumetinib consisted of 74 pediatric patients who received at least one dose ranging from 20 mg/m² to 30 mg/m² orally twice daily. Seventy-four percent of patients were exposed to the drug for greater than 2 years, and 23% were exposed for greater than 4 years. The safety population also included additional data from adult and pediatric patients who received selumetinib administered at various doses across a range of tumors in other clinical trials. In a single arm trial, there are no comparisons to be made; however, the safety profile of the drug is consistent with the known safety profile of MEK inhibitors, and the drug has been appropriately labelled for both class effects of the drug and adverse reactions observed in the pediatric population. • A risk evaluation and mitigation strategy (REMS) is not recommended for selumetinib given the current safety profile and the experience of the medical community in managing expected MEK inhibitor toxicities. Given the intended chronic use of the drug for pediatric patients with NF-1 PN, postmarketing requirements will be imposed for long-term monitoring of patients to include evaluations for safety, growth and development. Risk management based on labeling as well as routine and enhanced	The safety profile for selumetinib is acceptable for the treatment of pediatric patients 2 years of age and older with neurofibromatosis-1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN) a non-malignant disease that causes severe morbidity.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	pharmacovigilance will be employed to ensure the safe and effective use of selumetinib in the indicated population.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

✓	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☒ Clinical outcome assessment (COA) data, such as	Sections 8.1.2, 8.1.6, 8.1.7
	☒ Patient reported outcome (PRO)	see above
	☒ Observer reported outcome (ObsRO)	see above
	☒ Clinician reported outcome (ClinRO)	see above
	☒ Performance outcome (PerfO)	see above
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☒ Natural history studies	7.0, 8.1.6, 8.1.7, 8.4
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	

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☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

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Clinical Team Leader/Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Neurofibromatosis type 1 (NF1) is a rare, autosomal dominant disorder caused by germline mutations in the NF1 tumor suppressor gene, which encodes the tumor suppressor protein neurofibromin 1. In the United States (US), NF1 has a prevalence of approximately 1 in 2700 (Gutmann et al 2013a, Monroe et al 2017) and a birth incidence of approximately 1:3000 (Ferner et al 2007). Approximately half of NF1 cases are familial, with penetrance being 100%, and the remainder are the result of de novo (spontaneous) mutations (Evans et al 2010). The diagnostic criteria for NF1 were defined at a National Institute of Health (NIH) consensus development conference in 1987 (National Institutes of Health Consensus Development Conference Statement 1987). In most cases, the diagnosis of NF1 is made on clinical grounds, requiring 2 or more clinical features to be present from the defined list of diagnostic criteria for NF1 presented below.

- Six or more café-au-lait macules (diameters ≥ 0.5 cm in pre-pubertal patients or ≥ 1.5 cm in post-pubertal patients)
- Two or more neurofibromas or 1 plexiform neurofibroma (PN)
- Freckling in axilla or groin
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia or thinning of long bone cortex)
- First-degree relative with NF1 (diagnosed using the above criteria)

NF1 is a progressive multi-system disease characterized by progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and the associated morbidities can be severe. Loss of NF1 function favors the GTP-bound active form of RAS, resulting in activation of the RAF/MEK/ERK pathway, which can be the cause of or sustain the growth of various tumor types, such as benign or malignant tumors. Patients with NF1 have an increased risk of developing tumors of the central and peripheral nervous system. PNs are one of the most common benign tumors, which occur in approximately 20% to 50% of NF1 patients (Korf 1999, Mautner et al 2008).

PNs are nerve sheath tumors that typically grow along large nerves and plexuses and are present at birth (Hannema and Oostenbrink 2017). PNs may develop along nerves anywhere in the body, and may be located around the orbit, face, upper and lower limbs, back, thorax,

abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion [ROM]), pain, respiratory impairment, visual dysfunction, and neurological dysfunction.

PN manifestations vary in type and severity. They may continue to become apparent through late adolescence and early adulthood (Williams et al 2009). PN can have heterogenous, complex shapes and sometimes reach very large size, with some documented as being 20% of body weight (Korf 1999, Mautner et al 2008). Patients may have more than one PN, each resulting in different signs and symptoms. PN grow most rapidly during the first decade of life and whilst growth rate is highly variable between patients, the growth rate of PN in younger children is generally much greater compared with that in older children or adults (Dombi et al 2007, Nguyen et al 2012, Tucker et al 2009). A Natural History study of NF1 conducted by the National Cancer Institute (NCI) Pediatric Oncology Branch (POB) has demonstrated that, although spontaneous PN shrinkage occurred in a small number of PN in older adolescent and adult patients, the shrinkage is very slow, over many years and no patient had spontaneous PN shrinkage of $\geq 20\%$ within a year (Dombi et al 2007, Gross et al 2018). Although PNs are benign tumors there is potential for them to undergo malignant transformation; malignant peripheral nerve sheath tumors (MPNST) associated with NF1 most commonly arise in pre-existing PNs (Gutmann et al 2017).

Once PN-related symptoms or morbidities have developed, spontaneous resolution has been shown to be extremely unlikely (Gross et al 2018). Chronic pain in NF1 can be associated with PN, as well as subcutaneous neurofibroma and bony deformations (scoliosis and pseudoarthrosis), and as such, can occur anywhere in the body or multiple sites at the same time (Bellampalli and Khanna 2019).

Importantly, PN can result in life-threatening complications due to compression of vital structures (e.g., great vessel compression, spinal cord compression, and airway obstruction). A retrospective data analysis of the clinical records of children with NF1 reported an increased mortality rate in children with symptomatic PN compared to those without PN or with unrecognized/asymptomatic PN. In this study, non-malignancy-related causes of death in patients with NF1-PN included hypovolemic shock due to a PN-related hemothorax and respiratory failure due to airway compression (Prada et al 2012).

Hence, symptoms from PN affect children from early childhood through adolescence and their entire lifespan, and these clinical complications not only have a considerable effect on patient daily life and can have potentially life-threatening or debilitating consequences but also imposes a societal burden.

In children and adolescents with NF1, research findings indicate reduced quality of life (QOL) relative to population norms and parent-reported ratings tend to yield lower scores in several

domains than child self-report (Garwood et al 2012, Gutmann et al 2017, Oostenbrink et al 2007, Sanagoo et al 2019). A study by Lai et al (2019) investigated health-related quality of life (HRQOL) in the more specific population of 140 children with NF1-related PN. These children reported worse scores than the population norms in the majority of domains, including those relating to physical function, mental health, and social function. Worse depressive symptoms, fatigue and pain interference were reported by children with more PNs (1 to 5 PNs compared to only 1 PN). Furthermore, Wolters et al (2015) found that worse overall QOL was reported in children and adolescents with NF1-PN who had more severe symptoms compared to those with mild symptoms. In addition, with excision of multiple neurofibromas and reconstructive surgery for PN reported as leading reasons for hospitalization in NF1 patients, increasing costs to the health care system should be recognized as an impact to the society (Wolkenstein et al 2000).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of NF1 and NF1 associated PN and emphasizes that although the disease is heterogeneous with regard to number of tumors per patient, size, growth rate, and resulting clinical manifestations, a key characteristic of all PNs is the rare occurrence of spontaneous regression.

PN-associated morbidity depends on the location of the tumor and compression of nearby structures. For example, orbital PNs can displace the globe and compromise vision; paraspinal tumors can compress the spinal cord and cause paralysis; PNs arising in the mediastinum may compress the trachea or great vessels leading to airway compromise; and tumors arising in the extremities can cause progressive neurologic deficit and pain. PNs can negatively impact overall growth and cause significant disfigurement in patients. Literature suggests that patients with symptomatic PN have increased mortality due to compression of airway and other vital structures. Further, although PN is a benign tumor, there is risk for malignant transformation to MPNST.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There is no approved treatment for NF1-related PN so treatment is either symptomatic (e.g., use of analgesics for pain amelioration) or involves the use of off-label agents which have demonstrated limited benefit (Jakacki et al 2017, Robertson et al 2012). Recently, off-label use of commercialized mitogen-activated protein kinase kinase (MEK) inhibitors has been observed (Papalia et al 2018, Vaassen et al 2019). In suitable patients, surgical excision of the PN may be performed.

Surgical excision is commonly triggered by neurologic, disfigurement, orthopedic, and airway clinical complications caused by PN (Prada et al 2012). However, for many patients surgery is not a viable option as most PNs 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); PN surgery is also associated with high risk of iatrogenic nerve injury and hemorrhage due to the invasiveness or high vascularity of the PN (Canavese and Krajbich 2011). Even with subtotal or partial PN resection, 18% of patients were reported to have experienced permanent surgical complications such as speech abnormalities, nerve palsies, and pain, with regrowth occurring in 55% of these patients (Prada et al 2012). Regrowth has been reported to commonly occur in patients under age 10 (Needle et al 1997). Thus, management of NF1 is often palliative and focused on alleviating symptoms with the use of pain control medications.

Data suggest that 12% of children with PNs take narcotics (Kim et al 2009) and over 70% of children and adults with NF1 use prescription pain medications (Créange et al 1999). Despite pain management being a crucial aspect of improving NF1 patients' QOL, no approved therapies exist for NF1-induced pain, and in the limited studies that evaluated the efficacy of analgesics or other pain management techniques in NF1, patients reported that available treatments were not beneficial. In total, 93% of NF1 adolescent patients with PN and 100% of their caregivers reported pain interference with daily functioning even after taking over-the-counter pain medications including acetaminophen, ibuprofen, and prescription pain medications including various opioids, anticonvulsants, antidepressants, anesthetics on a regular basis (Wolters et al 2015).

Treatment and clinical management options for NF1 PN are extremely limited. To date several Phase II clinical studies of targeted agents for progressive PN in children and young adults with NF1 have failed to demonstrate consistent or durable PN volume decreases (Gutmann et al 2013a). There are no approved medical treatments in the US or worldwide that have been shown to prevent, cure, slow, or reverse the growth of NF1-related PNs. Therefore, there is a recognized need for a safe and efficacious medicine for patients with NF1, particularly for those with significant morbidity due to growth of PNs.

The FDA's Assessment:

The FDA agrees with the Applicant's discussion of current treatment options for patients with NF1 PN and has the following additional comments.

There are currently no FDA-approved systemic therapies for treatment of PN. Off-label use of cytotoxic chemotherapy is generally not recommended due to risk for secondary malignancies and other safety concerns in a population with a benign tumor. Activity-estimating studies of various tyrosine kinase inhibitors, mTOR inhibitors, a farnesyltransferase inhibitor, and anti-inflammatory and immune modulating agents have not demonstrated meaningful or durable objective responses in patients with progressive PN (Jakacki et al 2017, Kim et al 2013, Robertson et al 2012, Weiss et al 2014, Widemann et al 2014).

Given the underlying pathogenesis of NF1, specifically the absence of functional neurofibromin and the resulting upregulation of RAS signaling of the RAF/MEK/ERK pathway, preclinical studies of drugs for NF1-related tumors have focused on agents that interfere with RAS and downstream pathways of RAS. MEK inhibitors have demonstrated antitumor activity in mouse models of NF1 PN, and there are case reports of off-label use of FDA-approved MEK inhibitors leading to objective responses in patients with PN (Jessen 2013, Papalia et al 2018, Vaassen et al 2019) . Multiple MEK inhibitors, including selumetinib, trametinib, binimetinib, and PD-0325901 are currently under investigation in ongoing clinical trials in pediatric and adult patients with NF1 PN and other NF1 related tumors (NCT03962543, NCT03231306, NCT02407405, NCT03363217, NCT03741101, NCT02124772).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Selumetinib is not currently registered (or approved) in the US or in any other part of the world. The current application was submitted by the Sponsor as a new drug application (NDA) on 13 September 2019.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

3.2. Summary of Presubmission/Submission Regulatory Activity

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Version date: July 24, 2019 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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The Applicant's Position:

Table 1 Major Regulatory Milestones for Selumetinib Development in Relation to Pediatric Neurofibromatosis Type 1

Date	Activity	Key Outcomes of FDA Interactions
IND 122851		
8 September 2014	Pre-IND/End of Phase I meeting; pIND 122851	Agreement on IND submission strategy.
17 July 2017	NF1 IND 122851 submitted	IND clearance for Intermediate Access Protocol (D1346R00002).
2 November 2017	Type C face-to-face meeting, to discuss the development plans for selumetinib for the treatment of pediatric patients with NF1-related PN	Agreement that data from SPRINT Phase II Stratum 1, with supportive data from SPRINT Phase I and the NCI POB NF1 Natural History study, may support regular approval of selumetinib. Agreement to perform independent review of the volumetric MRIs as a sensitivity analysis.
14 December 2017	Request for ODD	14 February 2018, ODD granted for selumetinib for NF1.
7 February 2018	FDA response to request for advice regarding pivotal (SPRINT) study data and DCO for potential NDA	Sponsor provided information from SPRINT Phase II Stratum 1 for feedback on the acceptability of data package to assess the benefit-risk profile in intended indication. FDA recommended that all patients with a confirmed response be followed up for at least 12 months from onset of response as determination of DCO to support a potential NDA.
18 July 2018	Type C meeting to discuss assessment of recently identified findings associated with SPRINT study, and planned mitigations	FDA generally agreed that AstraZeneca's plans to address potential issues appear reasonable; however, whether the mitigations can allow for full confidence in the reliability of the results to support marketing approval will be determined during NDA review.
17 October 2018	Preliminary BTM Request Advice submitted	FDA requested a summary of a correlation of the COAs with the tumor response and a summary of the DoR data.
28 November 2018	Preliminary BTM Request Advice Teleconference	Comments received during the teleconference were addressed in the BTM request.
30 January 2019	BTM request submitted	BTM granted 29 March 2019.
28 June 2019	Type B Pre-NDA/Breakthrough Therapy Strategy meeting.	Agreement on contents for full original application and timing of Rolling Review.
2 July 2019	Request for Rolling Review	Rolling Review granted 3 July 2019.
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26 July 2019	Wave 1 of Rolling Submission	NA
30 August 2019	Wave 2 of Rolling Submission	NA
5 September 2019	Wave 3 of Rolling Submission	NA
13 September 2019	Wave 4 of Rolling Submission	NA

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Date	Activity	Key Outcomes of FDA Interactions
27 September 2019	Application Orientation Meeting	NA

BTB Breakthrough Therapy Designation; COA Clinical Outcome Assessment; DCO Data cut-off; DoR Duration of response; FDA Food and Drug Administration; IND Investigational New Drug; MRI Magnetic resonance imaging; NCI National Cancer Institute; NDA New drug application; NF1 Neurofibromatosis type 1; ODD Orphan Drug Designation; PN Plexiform neurofibroma; POB Pediatric Oncology Branch.

The FDA's Assessment:

The FDA agrees with the Applicant's regulatory timeline and meeting types presented in Table 1 and provides the following additional comments regarding key discussions that occurred at specific meetings and other important regulatory submissions and communications prior to submission of NDA 213756.

Type B Pre-IND meeting - September 8, 2014

A pre-IND meeting was held among the FDA, the NCI, and the Applicant to discuss the development program for selumetinib for pediatric patients with inoperable NF1-related PN based on preliminary clinical results from the ongoing NCI-sponsored Study 11-C-0161 (CTEP#8799; SPRINT): "A phase 1 study of the mitogen activated protein kinase (MEK) 1 inhibitor AZD6244 hydrogen sulfate (selumetinib sulfate) in children with NF1 and inoperable plexiform neurofibromas." This study was conducted under IND (b) (4) NCI, with the support of the Applicant, proposed to amend the ongoing SPRINT study with the incorporation of a single arm expansion cohort to further investigate the safety and effectiveness of selumetinib in pediatric patients with NF1-related PN. The proposed primary endpoint was radiographic response using volumetric MRI analysis according to Response Evaluation in Neurofibromatosis and Schwannomatosis (REINS) criteria. The Applicant also proposed to measure clinical outcome assessment (COA) endpoints as exploratory endpoints to further characterize the benefit:risk profile and stated in the meeting briefing document that these results would not be included in product labeling claims. The results of the proposed expansion arm were intended to support a marketing application for selumetinib in pediatric patients with inoperable NF1 PN. NCI also provided supportive preliminary data from the ongoing NCI POB NF1 Natural History study. The following key points were discussed:

- The FDA stated that if the prospectively collected data from the ongoing NCI natural history study demonstrate a consistent PN growth rate, evidence that spontaneous tumor regression does not occur, and that improvement or worsening in measurable functional impairments correlate with decreases or increases, respectively, in tumor volumetric changes of $\geq 20\%$, this information could be sufficient to establish the natural history of the disease such that observed effects during the proposed study could be attributed to the selumetinib treatment effect and not the natural history of disease.
- The FDA stated that for the proposed 20% reduction in tumor volume to be considered clinically relevant, it will be essential to show that this change in volume is reliably

accompanied by a detectable effect on physical function or other measures indicating that the patient's quality of life is improved. The FDA acknowledged that the protocol could include multiple COA tools for supportive efficacy assessments due to various tumor locations (e.g., vision testing for orbital tumors, strength testing for spinal tumors, photography for disfiguring lesions, etc.) such that there would likely be more than one set of COA criteria incorporated into the protocol.

- FDA stated that given the rarity of NF1 PN, lack of treatment alternatives, and the debilitating complications arising from progressive PN, and provided that the natural history of disease has been adequately established through the NCI natural history study, a single-arm trial could support an application seeking marketing approval if the study demonstrates unequivocal evidence of an important treatment effect that results in an improvement in PN-related functional impairment or other well-characterized signs or symptoms of progressive PN disease. The FDA emphasized that the results of the trial must also demonstrate that treatment responses are sufficiently durable, considering the long-term survival of patients with NF1 PN.

On September 4, 2015, the SPRINT study under NCI-sponsored IND (b) (4) was amended to include the phase 2 expansion cohort discussed at the preIND meeting. The amended study included two groups within the expansion phase: Stratum 1 was for the enrollment of 50 patients with a measurable PN-related morbidity, and Stratum 2 was for the enrollment of 25 patients without significant PN-related morbidity at enrollment but whose tumors impose risk for development of morbidity. The primary endpoint was ORR according to MRI volumetric analysis using REiNS criteria.

Type C Meeting – November 7, 2017

A Type C meeting between the FDA and the Applicant was held to discuss the Applicant's planned analyses for ORR, duration of response (DOR), safety, and COA endpoints from the SPRINT trial in preparation for submission of a marketing application. The following key points were made:

- The FDA agreed that the planned descriptive analyses of the changes in the various COAs could be used as supportive data in characterizing the clinical benefit of selumetinib. The FDA stated that the proposed COAs were considered exploratory in the single-arm trial design and were unlikely to support labeling claims.
- The FDA recommended an additional response analysis be conducted after all patients had prolonged follow-up (i.e., at least 12 months from the onset of response) to better characterize the ORR and durability of response.

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- FDA stated that the general expectation for imaging endpoints used in a single-arm trial intended to support approval is blinded, independent confirmation of the ORR and DOR results.

Type C Meeting – July 18, 2018

A Type C meeting between the FDA and the Applicant was held to discuss potential trial conduct and data quality issues based on the Applicant's conduct of quality assurance audits of the SPRINT trial sites and the proposed risk mitigation plans to ensure reliability of the data. One concern was that a subset of patients had a portion of protocol-required safety assessments at local centers rather than at the SPRINT trial sites for patient convenience. The Applicant agreed to conduct and submit subgroup safety analyses for patients who received study-related evaluations at one of the trial clinical sites and for patients who had non-re-staging visits at local centers. The FDA generally agreed with the other proposed plans to address potential trial conduct issues and stated that whether the mitigation procedures can allow for full confidence in the reliability of the results to support marketing approval will be determined during review of the application.

Type C Meeting – November 13, 2018 (Written Response)

On August 29, 2018, the Applicant submitted a pre-NDA meeting request. The final topline results for DOR from SPRINT were not available. As such, the FDA could not agree to the final content of the planned NDA submission and therefore granted a Type C guidance meeting. Written responses to the Applicant's questions regarding the structure, format and content of the future selumetinib NDA submission were issued on November 13, 2018. The following key agreements and recommendations were made:

- The FDA agreed with the Applicant's plan to analyze ORR according to the REiNS volumetric MRI response criteria based on a blinded, independent review of images, the Applicant's analysis of the NCI central review of tumor volume data to derive ORR and DOR, and the original central NCI assessment.
- The FDA noted that the results of the independent review of ORR and DOR would likely be used as the primary regulatory analysis in the context of a single-arm trial.
- The FDA agreed with the Applicant's proposal to not pool the efficacy data from the phase 1 and 2 parts of the SPRINT study due to differences in design and patient characteristics; however, recommended that the Applicant conduct supportive efficacy analyses using SPRINT phase 1 results, and that these analyses be submitted and presented in the Summary of Clinical Efficacy (SCE).
- The FDA stated that the Applicant's plan to reference tumor volume data from the NCI NF1 Natural History study and the placebo arm from Part A of the NCI Study 01-C-0222 as

external controls for tumor growth and for the efficacy endpoints progression free survival (PFS) and time to progression (TTP), respectively was acceptable but noted that these analyses would be considered exploratory.

- The FDA stated that the Applicant’s proposal for the analyses of COAs based on the descriptive statistics and mixed model repeated measures (MMRM) appeared acceptable but noted that the open-label trial design limits interpretability of COA data because of patient’s (or parent/caregiver’s) knowledge of treatment assignment, lack of a comparator, small sample size, and potential instrument limitations. The FDA acknowledged the challenges of measuring clinical outcomes in diseases that are rare and heterogeneous across patients and stated that submitted COA data would be reviewed as part of the totality of data.
- The FDA agreed with the proposal to submit individual patient reviews (IPRs) as supportive efficacy data. The reviews were to include relevant COA results in the context of radiographic response data for each patient. The FDA advised that in each IPR, the Applicant include a discussion of how the change in the target function or symptom correlated with the radiographic response assessment. The FDA also requested that each IPR include a discussion of the patient’s safety and tolerability of selumetinib to allow for an individual benefit: risk assessment.

Breakthrough Therapy Designation – March 29, 2019

On January 30, 2019, the Applicant submitted a Breakthrough Therapy Designation (BTD) Request for selumetinib for the treatment of pediatric patients aged 3 years and above, with NF1 symptomatic and/or progressive, inoperable PN. The primary data supporting the BTD request for selumetinib came from 50 patients enrolled in SPRINT Phase 2, stratum 1. The FDA considered the data provided in the BTD request to be preliminary clinical evidence of a substantial improvement over the local control surgical options and supportive care therapies available for inoperable and morbid PN. The effect sizes on ORR and DOR were noted to be substantially larger than those observed in clinical studies of other products evaluated in similar study populations using the same volumetric response criteria. Additionally, the Applicant submitted preliminary results for pain and motor dysfunction evaluations from a subset of patients in SPRINT that suggested trends of improved strength and motor function and decreases in pain that correlated with reductions in tumor volume during selumetinib exposure. The FDA additionally considered published results from the NCI Natural History study suggesting that increases in tumor volume correlate with increased patient morbidity and that symptomatic patients generally do not have improvement in tumor related morbidity when there is no change in tumor volume. On March 29, 2019, the FDA granted BTD to selumetinib for the treatment of pediatric patients aged 3 years and above, with NF1 and inoperable PN that is causing significant morbidity.

Type B Pre-NDA meeting - June 28, 2019

A Type B Pre-NDA meeting was held among the FDA, the NCI, and the Applicant to come to agreement on the format and content of the complete application. The following key points were discussed:

- The FDA agreed that the efficacy data from SPRINT Phase II Stratum 1, including ORR, DOR, and COA results, could support filing of a marketing application for selumetinib for the treatment of pediatric patients with NF1 and inoperable PN that is causing significant morbidity. The FDA stated that the final indication would depend on review of the safety and efficacy data for all patients and relevant subgroups.
- The FDA agreed with the Applicant's plan to conduct and submit a supportive efficacy analysis comparing the SPRINT Phase II Stratum 1 response results to the proposed external control data from the NCI POB NF1 Natural History Study.
- The FDA did not agree to the Applicant's proposal to exclude SPRINT Phase II Stratum 2 efficacy and safety data from the NDA submission. During the meeting discussion, the FDA acknowledged that efficacy data from this cohort may be difficult to compare to the efficacy data from Stratum 1 due to shorter follow-up but asked the Applicant to provide preliminary ORR and DOR data from Stratum 2 in the 90-day safety update. The Applicant agreed to submit these data with the 90-day safety update. The FDA agreed with the Applicant's proposal to provide SAE line listings as the only safety data from Stratum 2 in the NDA with an update to these listings as part of the safety update.
- The FDA did not object to the Applicant's proposal to retain the NCI central analysis of ORR and DOR as the primary endpoint; however, reiterated that the FDA generally considers the results of independent review of ORR and DOR to be most free of bias and therefore most relevant for inclusion in product labeling. The FDA recommended that the Applicant provide, in the NDA, a rationale for their selection of the NCI central analysis of ORR and DOR as the primary efficacy analysis.
- The FDA acknowledged the multifactorial nature of detected changes in COAs during the study, but emphasized that in order to demonstrate a favorable benefit:risk assessment for selumetinib in a benign condition in which tumor shrinkage will not be predictive of improved survival, there should be a general correlation between decrease in tumor volume and improvement in disease-related functional impairment, symptoms, or an improvement in disfiguring tumors, to make the ORR results clinically relevant.
- The FDA stated that the acute and long-term safety of selumetinib in the intended patient population will also be considered in the overall benefit:risk assessment.

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4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspections by OSI were requested by the Division of Oncology 2. The objectives of inspections were to verify the ORR and DOR results as determined by the NCI central review and the independent review committee (IRC), to evaluate identification, documentation, and reporting of adverse events (AEs), and to assess general compliance with the SPRINT protocol.

Each site inspected was to be classified into one of the following categories:

- NAI = No deviation from regulations.
- VAI = Deviation(s) from regulations.
- OAI = Significant deviations from regulations. Data unreliable.

Three sites from the SPRINT trial were selected by the clinical review team for inspection by OSI. All inspected sites were classified by OSI as no deviation from regulations/no action indicated (NAI).

4.2. Product Quality

The quality review included drug product, drug substance and biopharmaceutical review teams. No major quality issues were identified, and approval of the NDA for selumetinib capsules, 10 mg and 25 mg was recommended. See the Office of Product Quality review for specific details.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Selumetinib (AZD6244) is an orally bioavailable, non-ATP competitive kinase inhibitor that targets mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinases 1 and 2 (MEK1/2); the established pharmacological class is kinase inhibitor. MEK1/2 are ubiquitously expressed proteins that are part of the Ras-Raf-MAPK-ERK signaling transduction cascade. Activation of the Ras-MAPK signaling pathway leads to proliferation in a large number of cancer types. Neurofibromatosis type I (NF1) is a syndrome caused by germline mutations in the *NF1* gene that result in widespread phenotypic outcomes, including plexiform neurofibromas. *NF1* codes for the protein neurofibromin, a widely expressed Ras GTPase activating protein (GAP). Ras GAPs catalyze the conversion of Ras from the GTP-bound active conformation to the GDP inactive conformation, thereby limiting downstream Ras signaling. Mutations in *NF1* commonly lead to increased Ras pathway signaling and dysregulated growth. Blocking downstream Ras signaling by targeting MEK1/2 may help circumvent the effects of losing neurofibromin GAP activity Kiuru, M and Busam, KJ (2017), including slowing or reducing plexiform neurofibroma growth.

In in vitro assays, selumetinib was able to inhibit the activity of purified MEK1 enzyme with IC₅₀ values of between 10-14 nM but was inactive, or only minimally active, against a panel of other kinases at a concentration of 10 μM. Selumetinib had similar activity against both MEK1 and MEK2 in inhibiting the phosphorylation of inactive ERK2. The Applicant also demonstrated that the N-desmethyl selumetinib metabolite was able to inhibit MEK-mediated ERK phosphorylation at lower concentrations than selumetinib itself; the selumetinib amide metabolite also inhibited ERK phosphorylation but not at clinically relevant concentrations. In vivo, selumetinib reduced proximal nerve root sizes as well as the number and size of tumors in a *Nf1^{fl/fl};Dhh^{Cre}*, a mouse model which allows for targeted knockout of *NF1* and recapitulates the development of endogenous neurofibromas. These studies support the proposed mechanism of action of selumetinib and the proof-of-concept for the proposed pediatric indication.

The Applicant conducted several stand-alone safety pharmacology studies with selumetinib. At doses of up to 100 mg/kg selumetinib had no remarkable effects on open field behavior or respiratory parameters in Sprague-Dawley rats. In a cardiovascular safety study in Gottingen minipigs, oral administration of selumetinib twice daily had no remarkable effects on electrocardiograms or circulatory function (heart rate, systolic and diastolic blood pressure) following limited dosing. These findings were consistent with the low potential for QT prolongation predicted by an in vitro hERG assay (IC₅₀>10 μM) as well as the lack of cardiac findings in the long-term monkey toxicology study. Minimal to mild mineralization associated

with elevated serum phosphorous was frequently present at multiple dose levels, particularly in rats and monkeys. In rats, this included moderate mineralization of the aorta at dose levels resulting in exposures ≥ 93 times the clinical exposure at the 25 mg/m² twice daily dose.

The Applicant evaluated the toxicity profile of selumetinib in rats, mice, and monkeys in GLP-compliant studies with durations of up to 3 months (rats) and 26 weeks (mice and monkeys). The Applicant chose the mouse as the rodent species for the long-term toxicology and developmental studies due to detectable levels of the active N-desmethyl metabolite in this species that allowed for toxicological coverage; there were no unique human metabolites or other metabolites that needed toxicological coverage in animals. The gastrointestinal (GI) tract was a major target organ in all 3 species. In stand-alone single-dose safety pharmacology studies in rats selumetinib induced dose-dependent gastric mucosal lesions and showed a mild increase in gastric motility. GI toxicity in the 26-week chronic mouse toxicology study ranged from mild inflammation and hyperplasia at the low dose of 1 mg/kg twice daily (approximately 2-3 times the human exposure based on AUC at the clinical dose of 25 mg/m² twice daily), to ulcerative lesions at the 20 mg/kg highest dose level. In the 3-month rat study, GI findings were primarily related to mineralization, while in monkeys there were clinical observations of watery-liquid stool and dehydration at selumetinib exposures greater than or equal to the clinical AUC at the 25 mg/m² twice daily dose. Gastrointestinal toxicity with diarrhea is a common clinical finding.

In addition to the GI tract, the other major target organs in the rodent toxicology studies were the skin and lower urinary tract. In the long-term 26-week toxicology study, mice received up to 20 mg/kg of selumetinib orally twice daily. Male mice did not tolerate the 20 mg/kg dose (approximately 33 times the human exposure at steady state of 1958 ng*h/mL at the clinical dose of 25 mg/m² twice daily), primarily due to urinary flow obstruction leading to death or early sacrifice of all males at the dose level by Week 16. In rats, the highest levels of tissue mineralization were in the kidneys. Clinical observations of skin lesions and scabs correlated with histopathologic findings of skin ulcerations and contributed to the termination of the rat study at selumetinib dose levels ≥ 20 mg/kg. Elevated neutrophils and monocytes in rats were most likely secondary to inflammatory responses due to skin lesions/scabs and ulcerations. Skin toxicity is also a common clinical finding.

While the plexiform neurofibromas associated with NF1 can be debilitating, they are generally slow growing and not immediately life-threatening (depending on location). Because of these characteristics, the Applicant conducted a full battery of reproductive toxicology studies as well as carcinogenicity studies to support the development of selumetinib. The Applicant assessed the effects of selumetinib on reproduction and development using mice, as mice, unlike rats, make the active N-desmethyl AZD6244 metabolite at detectable levels. Administration of selumetinib for 10 weeks had no effect on male fertility based on sperm counts and motility as well as fertility indices in untreated females paired with the treated males. At exposures higher

than clinical exposures, selumetinib did not have any clear effects on fertility indices in female mice treated for 2 weeks prior to mating through 6 days post-coitum. Selumetinib did, however, have developmental effects in both embryo-fetal development and pre- and postnatal development studies. In the embryo-fetal development study, doses greater than the lowest tested dose of 2.5 mg/kg twice daily (~5 times the human exposure based on AUC at the clinical dose of 25 mg/m² twice daily) selumetinib caused increased post-implantation loss, decreased fetal weights, and unossified or incompletely ossified skull bones as well as an increased incidence of cleft palate and open eyes. The Applicant attributed the incidence of open eyes at the 2.5 mg/kg dose level of selumetinib to a dosing error, resulting in the delivery of a higher dose at a critical timepoint for eyelid development. While FDA does not dispute this attribution, there were also findings of prematurely open eyes in the postnatal development study even at the lowest maternal dose level of 0.5 mg/kg twice daily (dam plasma concentrations 2 hours post-dose on lactation Day 4, of ~0.6 times the human C_{max} at the clinical dose of 25 mg/m² twice daily), suggesting that there is some potential for ocular effects at even lower doses of selumetinib. Findings in fetuses from dams at the high dose level of 37.5 mg/kg twice daily also included an increased incidence of folded retina and changes to the consistency of the lens. Similarly, in the pre- and postnatal development study there were dose-dependent increases in the number of litters with fetuses that had prematurely open eyes at doses ≥ 0.5 mg/kg as well as a decrease in the number of pups with pupil constriction on post-natal Day 21. While ocular effects were not clear in the nonclinical toxicology studies in adult animals, ocular toxicity does occur clinically with selumetinib and other MEK inhibitors. In addition, there are literature reports supporting a role for MAPK signaling, particularly after activation through FGFR receptors, in protecting/maintaining retinal pigment epithelial cells (Guillonneau, X. et al. 1998; Rosenthal, R. et al. 2005; and Van der Noll, R. et al. 2013). Finally, at maternal selumetinib doses ≥7.5 mg/kg (approximately equal to the clinical exposure at 25 mg/m² twice daily) there were decreased fetal weights at birth; body weights in these pups remained lower during the post-weaning period. The Applicant also demonstrated that selumetinib was present in milk in this study: selumetinib was detectable in untreated pups from treated dams 2 hours post-dosing on postpartum Day 4, at plasma concentrations of ~0.09 times the C_{max} at the clinical dose.

In genetic toxicology studies, selumetinib was positive in the in vivo mammalian erythrocyte micronucleus test at dose levels >160 mg/kg for the free-base formulation or 24 mg/kg for the hyd-sulfate formulation (both doses resulting in maximal concentrations or estimated maximal concentrations >38 times the C_{max} at the 160 mg twice daily clinical dose), but negative in both the presence and absence of metabolic activation for mutagenicity in the in vitro Ames Assay and for chromosomal aberrations in the in vitro mammalian cell gene mutation assay using the L5178Y/TK+/- mouse lymphoma cells. Selumetinib had no carcinogenic potential in dedicated studies in mice and rats.

Because the positive genotoxicity findings occurred only at doses approximately 40 times

higher (based on BSA) than the clinical dose and considering that the drug was negative in carcinogenicity studies, FDA made recommendations for use of effective contraception and avoidance of breastfeeding during treatment with selumetinib and for 1 week following the final dose, consistent with the recommendations described in the FDA guidance, Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations, for a non-genotoxic drug. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of selumetinib for the treatment of patients with NF1 who have symptomatic, inoperable plexiform neurofibromas.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA concurs

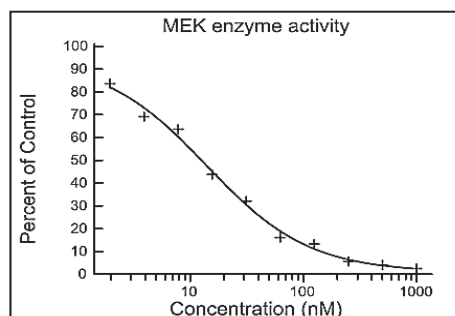
5.3. Pharmacology

Selumetinib (formerly known as AZD6244, AZ12252244, and ARRY-142886) has been evaluated in a comprehensive package of in vitro and in vivo nonclinical studies that were designed to characterize the pharmacology, safety pharmacology, pharmacokinetics (PK) and toxicology of this compound. Two forms of selumetinib have been used in the nonclinical development studies. Pharmacology (primary and secondary), and safety pharmacology studies were conducted using selumetinib free base. Due to the limited solubility of the selumetinib free base and the resulting low bioavailability, selumetinib hydrogen sulfate salt (hyd-sulfate) was developed and used in later studies. Selumetinib has an active metabolite, N-desmethyl selumetinib, which has also been characterized throughout nonclinical development.

Primary Pharmacology

The Applicant evaluated the enzymatic activity of purified constitutively active MEK1, in the presence of increasing concentrations of selumetinib (AZD6244), by measuring the incorporation of [γ -³³P]phosphate from [γ -³³P]ATP into ERK2 (Pharmacology Report #01; Yeh, TC. et al (2007); Clin Cancer Res 13:1576-1583). AZD6244 demonstrated concentration-dependent inhibition of MEK enzyme activity (Figure 1). The IC₅₀ was 14.1 nM (n = 9). Evaluation of the selectivity of AZD6244 (10 μ M) against a panel of 40 other serine/threonine and tyrosine kinases showed minimal or no inhibition. In the presence of increasing concentrations of ATP, AZD6244 was non-competitive with respect to ATP (data not shown).

Figure 1 Inhibition of MEK1 Enzyme Activity in the Presence of Increasing Concentrations of Selumetinib



(Applicant Figure excerpted from Yeh, TC. et al (2007); Clin Cancer Res 13:1576-1583)

In Pharmacology Reports #45 and #46, the Applicant confirmed the ability of AZD6244 to inhibit the ability of both MEK1 and MEK2 to phosphorylate ERK using two assays: the Z'-LYTE® biochemical assay which employs a fluorescence-based, coupled-enzyme format, based on the differential sensitivity of phosphorylated and non-phosphorylated peptides to proteolytic cleavage (Assay 1) and the radiometric assay described above to measure the phosphorylation of ERK1/2 (Assay 2). AZD6244 prevented phosphorylation of ERK by both MEK1 and MEK2 with similar potency (Table 2).

Table 2 In vitro Inhibition of MEK1 and MEK2 Enzyme Activity by AZD6244

Assay	MEK Isoform	IC ₅₀ (µM)
1 ^a	MEK1	0.222
1 ^a	MEK2	0.389
2 ^b	MEK1	0.417
2 ^b	MEK2	0.402

^a Invitrogen Z-LYTE assay (2 replicates)

^b Reaction Biology assay (4 replicates)

(Excerpted from the Applicant's submission)

Investigators further explored the ability of AZD6244 to inhibit MEK1/2 by measuring the phosphorylation state of ERK1/2 (phospho-ERK), the direct substrates of MEK1/2, in treated human cell lines (Pharmacology Report #02). AZD6244 inhibited ERK1/2 phosphorylation in 9 of 10 cell lines examined, with IC₅₀ values ≤10 nM (Table 3).

Table 3 IC₅₀ Values of Selumetinib for Inhibition of ERK1 and 2 Phosphorylation in Human Tumor Cell Lines

Cell line	Tumor type	IC ₅₀ (nM)
Calu-6	Lung	3.6
SKBR3	Breast	3.8
MDA-MB-231	Breast	7.4
Calu-3	Lung	1.8
SKOV3	Ovarian	40.8
Colo 205	Colorectal	5.4
MDA-MB-468	Breast	9.9
Saos-2	Osteosarcoma	5.3
DU-145	Prostate	5.5
BxPC3	Pancreatic	6.5

Each IC₅₀ value represents the average of 2 or 3 separate experiments, except for Saos-2 cell line which was tested only once.

Using the same methods, investigators assessed the ability of the N-desmethyl AZD6244 metabolite and the amide metabolite, to inhibit ERK proliferation in cell lines (Pharmacology Reports #05 and #08). N-desmethyl AZD6244 was more potent than AZD6244 in inhibiting phosphorylation of ERK in seven tumor cell lines (Table 4). In contrast, the AZD6244 amide was more than 30-fold less potent than AZD6244 (Table 5), suggesting that though this metabolite is active, it is unlikely to contribute significantly to the activity of AZD6244.

Table 4 Inhibition of ERK Phosphorylation by AZD6244 and N-desmethyl AZD6244

Cell line	IC ₅₀ (nM)		Ratio
	AZD6244	N-desmethyl AZD6244	
G361	8.98	2.64	3.4
A375	9.84	3.35	2.9
A2058	4.26	1.29	3.3
MelJuSo	4.40	1.08	4.1
MiaCaPa2	1.94	0.601	3.2
BxPC3	4.86	1.33	3.6
Panc-1	2.89	0.636	4.5

Table 5 Inhibition of ERK Phosphorylation by AZD6244 and AZD6244 Amide

Cell line	IC ₅₀ (nM)		Ratio
	AZD6244	AZD6244 Amide	
A375	23.69	913.9	38.6
A2058	20.15	784.9	39
Calu-6	15.04	759.2	50.5

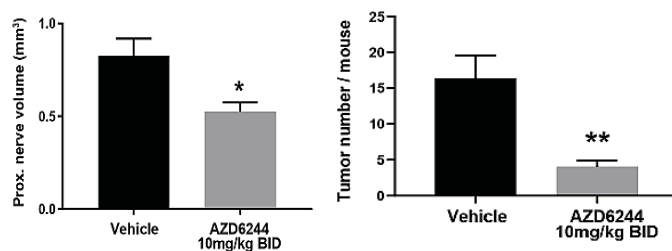
To further explore the ability of both AZD6244 and its N-desmethyl metabolite to inhibit MEK, investigators conducted an ex-vivo experiment using phorbol ester (TPA) to stimulate ERK phosphorylation in whole blood cells (Pharmacology Report #7). The N-desmethyl AZD6244 metabolite inhibited ERK phosphorylation at a slightly lower IC₅₀ than AZD6244 (Table 6), confirming the activity of both AZD6244 and this metabolite.

Table 6 Inhibition of TPA-Stimulated ERK Phosphorylation by AZD6244 and N-desmethyl AZD6244

Compound	IC ₅₀ (nM)
AZD6244	460
N-desmethyl AZD6244	266

The Applicant evaluated the in vivo antitumor effects of AZD6244 using the *Nf1^{flox/flox};Postn-Cre* mouse model of neurofibroma (Pharmacology Report #55). These mice are genetically engineered mice to lose *Nf1* gene expression in Schwann cell progenitors and develop neurofibromas with a histology that replicates human neurofibroma histology by 4 months of age. Four-month old *Nf1^{flox/flox};Postn-Cre* mice received AZD6244 (10 mg/kg) or vehicle orally twice daily for 12 weeks. AZD6244 reduced both the size of the proximal nerve roots (37% decreases compared to vehicle controls) and the tumor numbers (75% compared to controls) (Figure 2).

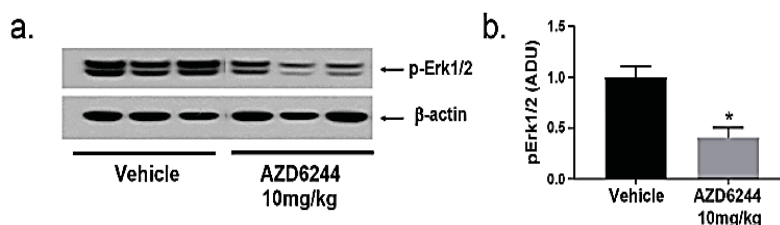
Figure 2 Effect of AZD6244 on Proximal Nerve Volume and Tumor Number in *Nf1^{flox/flox};Postn-Cre* Mice



(Applicant figure excerpted from Pharmacology Report #55)

Mice sacrificed 2 hours after administration of AZD6244 for evaluation of ERK phosphorylation by Western blot, showed approximately 60% inhibition of ERK phosphorylation compared to controls.

Figure 3 Inhibition of ERK Phosphorylation by AZD6244 in Neurofibroma Tumors from *Nf1^{flox/flox};Postn-Cre* Mice



(Applicant Figure excerpted from Pharmacology Report #55)

Secondary Pharmacology

Selumetinib and N-desmethyl selumetinib were tested at 10 μ M in a panel of in vitro radioligand binding and enzyme assays covering a diverse range of molecular targets, including enzymes, receptors, transporters and ion channels. Selumetinib had significant activity (defined as >50% inhibition) in 1 of the 305 assays in which it was tested (protein serine/threonine kinase PRKG1, 53% inhibition at 10 μ M). N-desmethyl selumetinib had significant activity in 1 of the 336 assays in which it was tested (protein serine/threonine kinase MEK1, 84% inhibition at 10 μ M).

The Applicant's Position:

In a secondary pharmacology panel of radioligand binding and enzyme assays, no targets were identified that were considered pharmacologically relevant for human therapeutic plasma exposure levels of selumetinib or N-desmethyl selumetinib.

The FDA's Assessment:

FDA confirmed the Applicant's findings. The screening assays covered a sufficient range of targets and did not demonstrate significant selumetinib or N-desmethyl selumetinib-mediated activity against proteins other than MEK1/2.

Safety Pharmacology

Central Nervous System

The effects of selumetinib on general behavioral, autonomic, neuromuscular and sensorimotor function and body temperature were assessed in an Irwin screen in conscious male rats (1758/ARR/03) for up to 24 hours after a single oral dose of 0 (vehicle), 10, 30 or 100 mg/kg selumetinib. There were no effects on body temperature or Irwin observations that were considered selumetinib-related. Therefore, the no-observed-effect-level (NOEL) was 100 mg/kg.

Cardiovascular System

In vitro evaluation (030819.BCP and 0179SZ): Selumetinib was tested for its effect on the human ether-à-go-go-related gene (hERG) encoded potassium channel over a nominal concentration range of 0.1 to 10 μ M. Selumetinib did not cause notable inhibition of the hERG current (mean $\pm$ SEM: 8.2% $\pm$ 0.8% inhibition at 10 μ M).

N-desmethyl selumetinib was tested for its effect on the hERG encoded potassium channel over a nominal concentration range of 0.03 to 100 μ M. N-desmethyl selumetinib did not inhibit the hERG current over this concentration range.

In vivo evaluation (Study 1759/ARR/03): The effects of selumetinib on arterial blood pressure (BP), heart rate and lead II electrocardiogram (ECG) (QT, heart rate corrected QT interval [QTc] and PR intervals) were determined. Cardiovascular parameters were monitored by telemetry from 4 male conscious Göttingen minipigs prior to, and up to 24 hours following the first administration of the day for each dose level. Each dose level of selumetinib was dosed twice daily (BID), with a minimum of 12 hours between the 2 administrations. Oral doses of 0 (vehicle control), 3, 10 and 30 mg/kg BID selumetinib were administered according to a cross-over design, with an interval of at least 2 days between dose levels.

Selumetinib total (and free, based on minipig protein binding of 93.7%) group mean plasma maximum observed plasma concentration (C_{max}) values were 92 (5.80), 126 (7.94) and 408 (25.7) ng/mL following administration of 3, 10 and 30 mg/kg BID selumetinib, respectively. There were no changes in cardiovascular parameters that were considered selumetinib-related. Therefore, the NOEL was 30 mg/kg BID.

Respiratory System

The effects of selumetinib on respiratory rate, tidal and minute volume, lung dynamic compliance and airway resistance were assessed in anaesthetized male rats (Study 1760/ARR/03) for up to 2 hours following a single oral gavage administration of 0 (vehicle), 10, 30 or 100 mg/kg selumetinib. Respiratory parameters were recorded in the spontaneously breathing rats via pressure transducers surgically placed in the trachea and plural cavity. Single oral administration of up to 100 mg/kg selumetinib produced no effect on tidal or minute volume, respiratory rate or lung dynamic compliance. At 100 mg/kg, airway resistance was slightly increased (18% compared to vehicle) only at the 2 hours post-dose time point. The NOEL was 30 mg/kg.

Gastrointestinal System

Gastrointestinal motility in rats (1761/ARR/03): The effects of selumetinib on gastrointestinal motility were assessed in male rats after a single oral dose of 0 (vehicle), 10, 30 or 100 mg/kg selumetinib. A charcoal suspension was administered orally 30-minutes post-dose, and the distance the charcoal travelled along the intestinal tract in 20 minutes was then measured. Selumetinib slightly increased the distance of charcoal meal travelled at the 3 doses tested. However, these effects were not statistically significant compared to vehicle and therefore were not considered to be related to selumetinib treatment. The NOEL was therefore considered to be 100 mg/kg.

Gastric irritation in rats (1762/ARR/03): The effects of selumetinib on gastric irritation were assessed in male rats after a single oral dose of 0 (vehicle), 10, 30 or 100 mg/kg selumetinib. Macroscopic evaluation for lesions in the stomach was made approximately 4 hours after dosing. Gastric mucosal lesions were observed at all dose levels. The incidence and severity of gastric findings was similar in animals dosed with vehicle or 10 mg/kg of selumetinib. In animals dosed 30 or 100 mg/kg selumetinib, there was an increase in the incidence and severity of gastric lesions, which at the 100 mg/kg dose, was similar to the positive control (aspirin 20 mg/kg followed by 1 mL/kg 0.4 molar hydrochloric acid). The NOEL was therefore considered to be 10 mg/kg.

Gastric secretion in rats (1763/ARR/03): The effects of selumetinib on gastric secretion were assessed in anaesthetized male rats after a single oral dose of 0 (vehicle), 10, 30 or 100 mg/kg selumetinib. Sixty minutes post-dose, animals were anaesthetized and prepared for assessment, and gastric secretion was subsequently evaluated by measuring the volume, pH and acidity of the gastric juices 4 hours later. Selumetinib had no effect on the gastric secretion parameters. The NOEL was 100 mg/kg.

The Applicant's Position:

Selumetinib has been evaluated in a battery of in vivo safety pharmacology studies to evaluate potential effects on the cardiovascular, respiratory, central nervous system (CNS) and

gastrointestinal function. Selumetinib and N-desmethyl selumetinib were also evaluated in a hERG assay and a secondary pharmacology panel of targets in vitro. There were no toxicologically significant findings in these studies and assays.

The FDA's Assessment:

FDA confirmed the Applicants' assessment that acute oral administration of selumetinib did not have any clear effects on neurological, cardiovascular, or respiratory parameters in rats or minipigs, but did affect gastrointestinal (GI) endpoints in rats. These GI effects included a mild increase in gastric motility at doses ≥ 10 mg/kg (Table 7); though this increase did not reach statistical significance) and a dose-dependent increase in mucosal lesions at doses ≥ 30 mg/kg.

Table 7 Mild Increases in Gastric Transport in Selumetinib-treated Animals

Treatment	Charcoal meal travel (%) Mean $\pm$ S.E.M.
Vehicle	61.3 $\pm$ 3.1
ARRY-142886, 10 mg/kg	69.7 $\pm$ 4.8
ARRY-142886, 30 mg/kg	67.8 $\pm$ 3.7
ARRY-142886, 100 mg/kg	71.9 $\pm$ 3.3
Atropine, 2 mg/kg	49.0 $\pm$ 1.3 *

(Applicant Table excerpted from Study#1761/ARR/03)

5.4. Absorption, Distribution, Metabolism, Excretion/Pharmacokinetics

Data:

Absorption

7 Day Oral Dose Range Finding Study in the Mouse (Study 0354DM)

The pharmacokinetics of AZD6244 and N-desmethyl-AZD6244 in the cynomolgus monkey following oral and intravenous administration (Study KKP023)

Selumetinib hydrogen sulfate (hyd-sulfate) showed higher exposure and approximately dose proportional increase in exposure compared with the free base which demonstrated dose limited absorption. In mice after 50 mg/kg BID dose of selumetinib hyd-sulfate time to maximum observed plasma concentration (t_{max}) was 3.8 hours and 1 hour respectively in males and females, with similar C_{max} of 55 and 63 $\mu\text{g/mL}$ and area under the plasma concentration-time curve from time 0 to 12 hours ($AUC_{(0-12)}$) 271 and 258 $\mu\text{g.h/mL}$ respectively. In monkey at 5 mg/kg t_{max} was 0.5 hours to 1 hour for the hyd-sulfate and mean C_{max} and area under the plasma concentration-time curve from time 0 to 24 hours ($AUC_{(0-24)}$) were 2.55 $\mu\text{g/mL}$ and 3.46 $\mu\text{g.h/mL}$, respectively with half-life of circa (approximately; ca.) 5.6 hours. The mean bioavailability was 56% with hyd-sulfate, compared to 29% for the free base.

Distribution

The in vitro binding of [¹⁴C]-AZD6244 to the plasma proteins of mouse, rat, dog, minipig, monkey and man and to specific plasma proteins and the association of [¹⁴C]-AZD6244 with the blood cells of rat, dog, monkey and man (Study KPJ003)

The tissue distribution of total radioactivity in the rat following oral administration of [¹⁴C]-AZD6244 (Quantitative whole-body autoradiography) (Study KMR002)

Plasma protein binding of [¹⁴C]-selumetinib was not dependent on concentration but varied between species: minipig (93.7%)<dog (94.6%)<monkey (97.7%)<human (98.4%)<mouse (98.9%)<rat (99.7%) (Study KPJ003). Plasma:whole blood ratios ranged from 1.9 in rat, 1.3 to 1.4 in dog, 1.3 to 1.5 in monkey and 1.4 to 1.8 in human, indicative that [¹⁴C]-selumetinib was predominantly distributed in plasma.

In pigmented and albino rats, the highest observed concentrations of radioactivity in the majority of tissues were measured at 1 or 8 hours post dose with tissue concentrations generally lower than blood and minimal penetration into the CNS (Study KMR002). Relatively higher concentrations of radioactivity were found in the lung, liver, kidney and adrenal gland at each timepoint. There was no evidence of high affinity melanin-specific binding of radioactivity in the pigmented tissues (pigmented skin and uveal tract). Levels of radioactivity in the uveal tract decreased over the course of the study and were not distinguishable from background at 72 hours post dose. The half-life of elimination of radioactivity from the eye (calculated from liquid scintillation counting data) was ca. 60 hours.

Metabolism

Metabolism of AstraZeneca [¹⁴C]-AZD6244 in rat, mouse, dog, monkey and human hepatocytes (Study KMN011)

Profiling and Characterization of Metabolites Following Administration of [¹⁴C]-AZD6244 to Healthy Volunteers (Study YAU169)

Comparison of the metabolites generated by each species hepatocytes after 180 minutes of incubation with [¹⁴C]-selumetinib (5 uM) as percent of chromatogram radioactivity.

Label (hADME)	Proposed Structure	Mouse	Rat	Monkey	Dog	Human 1 ¹	Human 2 ¹
Parent	Selumetinib	20.0	12.8	11.7	39.4	52.3	26.3
Peak B	N-desMe selumetinib amide glucuronide	5.07	1.03				2.62
Peak D (M2)	Selumetinib amide-glucuronide[-2H]	12.0	25.0	20.2	4.29	11.5	23.2
Peak E1 (M4)	Selumetinib-glucuronide		1.49	45.7	4.91	9.39	15.8
Peak E2 (M3)	N-desMe selumetinib glucuronide	8.22					
Peak F (M7)	Selumetinib-glucuronide	11.3	41.6	15.6	35.1	10.3	19.2
Peak G (M8)	N-desMe selumetinib	27.9			2.78	4.22	2.42

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Peak H	Unknown	6.33					
Peak K	Unknown	1.29	3.33	1.04	1.54	1.01	1.37
Peak L	Selumetinib carboxylic acid glucuronide		1.41			2.40	1.03
Peak M (M15)	Selumetinib carboxylic acid		2.55			3.18	1.37

¹ Two separate pools of human hepatocytes were used in this study. Peaks with an area less than 2% of the chromatogram radioactivity at all time points are not included. Metabolites without an 'M' label were not observed in human ADME study.

Labels correspond to study annotation and human ADME (YAU169) designation in parenthesis.

ADME Absorption, distribution, metabolism, excretion; hADME Human absorption, distribution, metabolism, excretion.

In vitro experiments indicate that selumetinib undergoes cytochrome P450 (CYP) enzyme mediated Phase I metabolic oxidation and extensive UDP-glucuronosyltransferase (UGT) enzyme mediated Phase II conjugation to form several glucuronide conjugates.

The radiolabeled [¹⁴C]-selumetinib human absorption, distribution, metabolism, excretion (ADME) study indicated that glucuronidation plays a significant role in the clearance (CL) of selumetinib, with 37% of total radioactivity in plasma assigned to glucuronide conjugates, 12% to residual CYP metabolites (which were not further metabolized through conjugation) and 40% as unchanged selumetinib.

The most abundant circulating metabolite in human (M2), was postulated to result from loss of the ethanediol moiety in combination with glucuronidation and an additional loss of 2 mass units. Full structural characterization of M2 confirmed that selumetinib had undergone cyclization to an imidazoindazole (M10), followed by glucuronidation. A further 6 metabolites were identified in human plasma, each accounting for between 2% and 7% of the circulating drug-related material (mean of all subjects), including metabolites resulting from N-demethylation in combination with the loss of the ethanediol moiety, glucuronidation and intramolecular cyclisation (M1, 3.5%), N-demethylation in combination with glucuronidation (M3, 2.5%), direct glucuronidation of selumetinib (M4, 7.1%), N-demethylation (M8; 2.9%), N-demethylation in combination with oxidation of the primary alcohol group to a carboxylic acid (M11, 3.6%) and a carboxylic acid resulting from hydrolysis of the amide group (M15; AZ13326637, 2.2%).

Excretion

The disposition of [¹⁴C]-AZD6244 in the rat following oral and intravenous administration (Study KMR006)

Following oral administration, the main route of excretion was via the feces, with mean recoveries of 91.8% and 101.6%, in males and females, respectively. Urinary excretion was 9.3% and 4.9%, respectively. Excretion of radioactivity was ca. 98% and 104% by 48 hours respectively.

Toxicokinetic data from general toxicology studies

<i>1-month and 6-month repeat dose studies in mouse (Study 0355AM and Study VKS/0211)</i> In 1-month study doses of ca. 11, 34 and 103 (reduced to 69) mg/kg BID gave C_{max} and $AUC_{(0-12)}$ values that were slightly greater than dose proportional with no accumulation across the study period. Exposure to selumetinib was similar in male and female mice. Male mice showed higher plasma concentrations of N-desmethyl selumetinib (C_{max} 1.7, 6.0, 7.4 $\mu\text{g/mL}$) than female (C_{max} 0.8, 2.4, 4.5 $\mu\text{g/mL}$) mice on Day 1 across the dose range but this difference had reduced by Day 28 when N-desmethyl selumetinib $AUC_{(0-12)}$ values were lower in comparison with Day 1. In 28-week study, mean selumetinib exposure was higher in female mice than in males at Weeks 1 and 4 and the difference was proportionately greater at higher dose levels. At most (Week 4 in 20 mg/kg) exposure was 2-fold higher in females than males. However, no accumulation occurred across the study period and the terminal elimination half-life of selumetinib was between 3.0 and 7.6 hours with no evidence of a sex-difference or change with duration of dosing. Exposure to N-desmethyl selumetinib was higher in male mice than in females. N-desmethyl selumetinib C_{max} and $AUC_{(0-12)}$ values were approximately 3% to 20% and 3% to 28% respectively of those of selumetinib in all dose groups. N-desmethyl selumetinib accounted for a lower proportion to selumetinib at 4 and 16/26 Weeks compared to Day 1. Half-life values for N-desmethyl selumetinib were between 2.9 and 7.1 hours with no evidence that the half-life for N-desmethyl selumetinib was longer than that for selumetinib.
Toxicokinetic data from reproductive toxicology studies <i>Oral Dose Range Finding Embryofetal Development Study in the Mouse (Study 0430RM)</i> <i>A Twice Daily Oral (Gavage) Developmental and Perinatal/Postnatal Reproduction Study in the Mouse, Including a Postnatal Behavioral/Functional Evaluation (Study 20082140)</i> Study 0430RM - Selumetinib C_{max} and area under the plasma concentration-time curve (AUC) values showed an approximately proportional increase with increasing dose across the entire dose range (2.2 to 79.2 $\mu\text{g/mL}$ and 10.3 to 576.7 $\mu\text{g}\cdot\text{h/mL}$ respectively). For N-desmethyl selumetinib there was a less than proportional increase (0.1 to 0.7 $\mu\text{g/mL}$ and 0.5 to 5.3 $\mu\text{g}\cdot\text{h/mL}$ respectively). Study 20082140 - Mean plasma C_{max} levels of selumetinib and N-desmethyl selumetinib at 2 hours post dose on Day 4 in F0 generation mice ranged from 0.45 (1 mg/kg/day) to 4.17 $\mu\text{g/mL}$ (15 mg/kg/day) and 0.14 (1 mg/kg/day) to 1.45 $\mu\text{g/mL}$ (15 mg/kg/day) respectively across the dose range. In F1 generation mice the mean plasma levels of selumetinib and N-desmethyl selumetinib at 2 hours post dose on Day 4 ranged from 0.07 (4 mg/kg/day) to 0.36 $\mu\text{g/mL}$ (15 mg/kg/day) and 0.007 (1 mg/kg/day) to 0.11 $\mu\text{g/mL}$ (15 mg/kg/day) respectively across the dose range.
Toxicokinetic data from carcinogenicity studies

6-month oral carcinogenicity study in CByB6F1/Tg rasH2 hemizygous mice and a 2-year oral carcinogenicity study in the rat (Study 20086561 and Study 501094)								
	Selumetinib				Selumetinib N-desmethyl			
	C _{max} (ug/mL)		AUC ₍₀₋₁₂₎ (ug.h/mL)		C _{max} (ug/mL)		AUC ₍₀₋₁₂₎ (ug.h/mL)	
	Males	Females	Males	Females	Males	Females	Males	Females
6-month oral carcinogenicity study with hyd-sulfate in CByB6F1/Tg rasH2 hemizygous male/female mice (Study 20086561) - Day 176								
3 mg/kg BID	1.8	2.4	5.7	10.8	0.4	0.3	1.4	1.9
8 mg/kg BID	4.9	10.4	14.6	38.4	1.0	0.7	2.9	3.7
25/15 mg/kg BID ¹	12.0	11.6	46.7	70.9	1.6	0.9	5.3	5.0
2-year oral (gavage) carcinogenicity study in the rat (Study 501094)²								
0.25 ³ /0.1 ⁴ mg/kg QD	0.44	0.29	6.91	3.57	BLQ	BLQ	BLQ	BLQ
0.8 ³ /0.3 ⁴ mg/kg QD	1.88	1.06	22.2	13.18	0.001	BLQ	0.003	BLQ
2.5 ³ /1 ⁴ mg/kg QD	6.54	4.32	80.09	61.79	0.005	0.012	0.036	0.201

¹ The dose level was reduced from 25 mg/kg BID to 15 mg/kg BID beginning on Week 19, Day 130, onwards.

² AUC₍₀₋₂₄₎ is reported.

³ Dose given to male rats.

⁴ Dose given to female rats.

AUC₍₀₋₁₂₎ Area under the plasma concentration-time curve from time 0 to 12 hours; BID Twice daily; BLQ Below limit for quantitation; C_{max} Maximum observed plasma concentration; hyd-sulfate Hydrogen sulfate; QD once daily.

The Applicant's Position:

Selumetinib shows improved absorption when administered as the hyd-sulfate salt with approximately dose proportional increase in exposure and no accumulation on repeated administration and moderate half-life in animals. The metabolism is well understood, showing that the most abundant circulating metabolite is an O-glucuronide conjugate of an imidazoindazole derived from selumetinib with loss of the side chain. Metabolism has been demonstrated to involve multiple pathways and enzymes including an appreciable level of glucuronidation. The active N-desmethyl metabolite, M8, was observed in both mouse and human together with several other metabolites. The majority of the drug was excreted in the feces as metabolites; only minor levels of unchanged selumetinib were excreted in the urine or feces.

The FDA's Assessment:

FDA confirmed the Applicant's representation of the ADME data based on the submitted reports and generally agrees with the presentation of the findings. In the pigmented rat tissue distribution study (KMR002), organs with relatively high radioactive exposure levels (levels similar to those in the organs listed as targets by the Applicant of liver, lung, kidney, and adrenal gland) included the heart, bladder wall, pancreas, and pituitary and thyroid glands). Consistent with oral administration, the highest, but transient, levels of radioactivity were present in the stomach.

In addition, the available data show that the active N-desmethyl selumetinib metabolite is present in mice and, based on the general toxicology data below, is present at high enough levels to cover the exposure of this metabolite in humans at the 25 mg/m² twice daily dose. The Applicant also conducted both an Ames assay and a hERG assay to further assess the safety of N-desmethyl selumetinib (negative predictions in both assays). Thus, there is adequate nonclinical data to support the safety of this metabolite. There are no unique human metabolites of selumetinib or metabolites which require additional toxicological coverage. No additional nonclinical ADME studies are warranted.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Two forms of selumetinib have been used in the nonclinical development studies. Initial studies were conducted using selumetinib free base, which was later replaced with selumetinib hyd-sulfate. The limited solubility of selumetinib free base resulted in a less than proportional increase in exposure and decreasing bioavailability with increasing dose in the nonclinical studies. The hyd-sulfate form demonstrated enhanced and dose-related increases in exposure in the nonclinical studies compared to free base. Only repeat dose studies conducted with selumetinib hyd-sulfate are included in this document as the toxicities observed in rodents and monkeys with selumetinib free base and selumetinib hyd-sulfate were relatively similar. Additionally, selumetinib hyd-sulfate is the clinically relevant form.

Nonclinical safety of selumetinib has been evaluated in pharmacologically relevant rodent (rats and mice) and non-rodent (cynomolgus monkeys) species. The minor (<10% of the total circulating drug product) human Phase I metabolite, N-desmethyl selumetinib (AZ12442942), is a pharmacologically active metabolite which is not produced to any significant extent in rats and monkeys, but is produced in CD-1 mice therefore, mouse was selected as the rodent

species for the 1-month, 26-week, and reproductive toxicology studies with selumetinib hyd-sulfate.

The nonclinical safety of selumetinib has been evaluated in repeat dose oral toxicity studies of up to 3 months in rats and up to 26 weeks in mice and monkeys; a battery of in vitro and in vivo genetic toxicity and carcinogenicity studies; reproductive toxicology studies and an in vitro phototoxicity assay. Potential genotoxicity of N-desmethyl selumetinib was also evaluated. The reversibility of selumetinib-related findings was evaluated in 1-month studies in mice and monkeys as well as in the 26-week study in mice.

All pivotal toxicology studies were appropriately designed in accordance with ICH guidelines and were conducted in compliance with GLP regulations.

Study Title/Number: 26-week Oral Toxicity Study in the Mouse with Assessment of Effects on Male Fertility Followed by a 13 Week Recovery Period (VKS/0211)

Key Study Findings:

- Early termination of 14 males at 20 mg/kg BID group was associated with inflammation and obstruction of the urinary tract.
- Gastrointestinal (GI) tract was identified as the major target organ in mice. The inflammatory and erosive/ulcerative changes 20 mg/kg BID group animals were associated with early decedents in several animals. Inflammatory cell infiltration of the portal area in the liver, reticulocytosis, splenic extramedullary hematopoiesis (EMH), and changes in hematological parameters were noted and considered secondary to erosive and inflammatory changes in the GI tract in mice.
- Tissue mineralization was restricted to minimal multifocal mineralization in the liver, in only a small number of animals at 20 mg/kg BID.

Conducting laboratory and location:

(b) (4)

Good Laboratory Practice (GLP) compliance:

Yes

Methods

Dose and frequency of dosing: 0 (vehicle), 1, 5, or 20 mg/kg BID (total doses of 0, 2, 10, and 40 mg/kg/day)

Route of administration: Oral (gavage)

Formulation/vehicle: 30% Captisol in water

Species/strain: Crl:CD1(ICR) mouse

Number/sex/group: 15M and 15F

Age: 40 to 47 days

Satellite groups/unique design: Toxicokinetic (TK) groups - 9M and 9F (vehicle group); 18M and 18F selumetinib treated groups; recovery group - 10/sex/group (0 and 20 mg/kg

BID); additional 5M (1 and 5 mg/kg/BID) for fertility assessment.
Undosed females were paired with study males on a 1:1 basis.
Assessment of male fertility after approximately 10 weeks of dosing by pairing of treated males from the study with untreated females on a 1:1 basis. To provide a reliable estimate of fertility, 5 males were included in the 1 and 5 mg/kg BID recovery groups. These additional 5 males at 1 and 5 mg/kg BID were terminated following examination of partner females.

Deviation from study protocol affecting interpretation of results: No

Observations and Results: Changes from Control

Parameters	Major Findings
Mortality	A total of 23 animals, 15M and 8F, died prematurely. All deaths at 20 mg/kg BID were considered to be selumetinib-related. The 20 mg/kg BID dose was not tolerated in the males and resulted in early deaths of 14 animals in Weeks 8 to 16 (main, recovery, and TK), and the premature sacrifice of the remaining males in this group after 15 weeks of treatment. The cause of death in the majority of these males was due to changes in the lower urinary tract. Premature death occurred in 1M and 6F at 20 mg/kg BID in Weeks 11 to 25 due to marked inflammatory changes in the large intestine.
Clinical Signs	Unscheduled death or termination: ↓ activity/unresponsiveness, piloerection, hunched posture, abnormal breathing, and pallor. Scheduled termination: Females at the 20 mg/kg BID - fast breathing and thin appearance. No treatment-related adverse clinical observations at other dose levels.
Body Weight	↓ Mean body weight gain (77% of control) in males at 20 mg/kg BID (Weeks 0 to 15). ↓ Mean body weight gain (56% of control) in surviving females at 20 mg/kg BID. ↓ Mean body weight gain (81% of control) in females at 5 mg/kg BID. No treatment-related effects on body weight gains in males and females at 1 mg/kg BID or males at 5 mg/kg BID.
Ophthalmoscopy	No selumetinib-related changes
Hematology	Mild to minimal transient ↑ in total white blood cell counts (neutrophil, eosinophil, monocyte, and large unstained cells) at all dose levels. Transient ↓ in hematocrit, hemoglobin associated with ↓ in mean cell hemoglobin, and mean cell volume at 20 mg/kg BID. ↑ in circulating red blood cells and ↑ in reticulocytes at 20 mg/kg BID.
Clinical Chemistry	At 20 mg/kg BID for 15 or 26 weeks ↓ in plasma albumin and A/G ratio (males & females); ↓ in plasma glucose (females); ↑ in plasma phosphorus, sodium, calcium (males), and changes in plasma urea (↑ males, ↓ females). Minor ↓ in phosphorus and albumin levels in males only at 5 mg/kg BID.

FDA Comment on Clinical Chemistry: At the 20 mg/kg dose level, the increases in phosphorous were 25% in males and 24% in females at Week 13 (mid-study). In surviving females at the 20 mg/kg dose, phosphorous remained high at Week 27.

Urinalysis	Slight changes in the group mean pH value (↓), urinary sodium (↑), and chloride (↑) concentrations at 20 mg/kg BID.

FDA Comment on Urinalysis: In males at the 20 mg/kg high dose level, urinary sodium and chloride were increased 23% and 47%, respectively, at the early group termination timepoint of Week 16.

Gross Pathology	In all but one of 14M at 20 mg/kg BID euthanized prematurely (Weeks 8 to 16) or found dead - obstruction of the lower urinary tract, which was considered to be the major factor contributing to the poor clinical condition or death of these animals; 1M had caecal ulceration. In 1M and 6F at 20 mg/kg BID prematurely killed/found dead (Weeks 11 to 25) - changes in the large intestine were considered to be the major factor contributing to the poor clinical condition and death. At scheduled necropsy (Week 27): - Thickening of caecum and colon, enlargement of spleen and enlargement of mesenteric lymph node at 20 mg/kg BID. - Enlargement of the mesenteric lymph node at 1 and 5 mg/kg BID.
Organ Weight	↑ spleen weights in females at 20 mg/kg BID.
Histopathology	Unscheduled termination at 20 mg/kg BID: Males (Weeks 8 to 16) - swelling, congestion, and/or hemorrhage of corpus cavernosum of the bulbocavernosus muscle, hemorrhagic, and inflammatory cell infiltration in the urethra, obstruction of the penile urethra, and marked distension of the urinary bladder; urethral obstruction resulted in backflow pressure leading to secondary changes in the ureters (distended), seminal vesicles (edematous), prostate (edematous), and kidney (enlarged, pelvic dilatation, ruptured); inflammatory changes in colon and duodenum of 3M. 1M and 6F (Weeks 11 to 25) - erosive and inflammatory changes in the large intestine including colon and caecum, with occasional perforation and/or involving the peritoneum; secondary changes to the intestinal inflammation in the liver, spleen, bone marrow, and lymph nodes; multifocal mineralization in the livers in 2M. Males (terminated after 15 weeks) with no signs of ill-health prior to sacrifice - findings in lower urinary tract (congestion of the corpus cavernosum of the bulbocavernosus muscle, inflammation/necrosis in the preputial glands, and marked urethral luminal dilatation in one animal) with no evidence of urethral obstruction or bladder distension; changes in the GI tract (inflammatory changes in the colon, caecum, rectum, and duodenum, sometimes associated with epithelial hyperplasia and/or mucosal ulceration and degeneration of the underlying muscular propria); pituitary gland (congestion), bone marrow (↑ granulopoiesis); spleen (↑ presence of granulocytes) and mesenteric lymph nodes (↑ level of plasmacytosis). Scheduled termination: 20 mg/kg BID females - erosive and inflammatory changes in the GI tract, with secondary reactive changes in the lymphoreticular system (↑ EMH in spleen;

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	↑ plasmocytosis in lymph nodes) and inflammatory cell infiltration of the portal area in the liver. 5 mg/kg BID - minimal to slight inflammation with hyperplasia in the colon, caecum, and rectum; and minimal multifocal mineralization in the liver in 1M. 1 mg/kg BID - minimal inflammation with epithelial hyperplasia in the colon in 1M and 2F.
Recovery	Full or partial recovery for most changes at the end of the 13-week recovery period. Minimal changes were seen in individual animals in the liver (multifocal mineralization), colon (inflammation), caecum (inflammation), spleen (↑ spleen weight, with no histological correlate). Only partial recovery in blood chemistry changes; plasma urea and phosphorous remained high in previously treated males and albumin and cholesterol levels were low in females, with A/G ratios were reduced in both sexes.
Mating Performance and Fertility	No selumetinib-related effects on male fertility at any dose level.

A/G Albumin:globulin; BID Twice daily; EMH Extramedullary hematopoiesis; F Female; GI Gastrointestinal; M Male; TK Toxicokinetic.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

FDA Assessment: FDA confirmed the Applicant’s presentation of the mouse toxicology data and in general agrees with the Applicant’s assessment; however, in addition to the GI tract, the lower urinary tract was a major target organ in male mice. Levels of neutrophils increased over time, possibly correlating with increased gastric lesions, and were up to 7.5 times the levels of control animals in high dose females at the end of the 26-week dosing period. As the C_{max} and AUC values are important for comparisons to clinical data and the Applicant did not include the toxicokinetic values in the PK section, that data is included here. Following repeated administration of AZD6244 to male and female mice, exposure (C_{max} and AUC) increased with increasing doses in Weeks 1 and 16/26 (Table 8), with larger increases in exposure to AZD6244 in females than males.

Table 8 26-Week Mouse Toxicokinetic of AZD6244

Dose Level (mg/kg, BID)	Sex	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-12h} µg•h/L	AUC _{0-∞} µg•h/L	T _½
Week 1						
1	M	1.8	0.67	4.5	4.8	3.5
	F	1.9	0.67	5.8	6.7	5.14
5	M	7.1	0.67	18.5	19.3	2.95
	F	11.7	0.67	35.5	43.2	5.86
20	M	29.6	0.67	82.0	90.7	4.3
	F	44.5	0.67	137	176.8	6.9
Week 26/16*						
1	M	1.0	0.67	3.9	4.2	3.2
	F	1.6	0.67	5.1	6.1	5.6
5	M	6.1	0.67	22.5	26.6	5.0

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Dose Level (mg/kg, BID)	Sex	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-12h} µg•h/L	AUC _{0-∞} µg•h/L	T _½
20	F	5.5	0.67	25.8	29.6	4.2
	M	17.9	0.67	65.0	91.9	3.8
	F	27.8	0.67	98.9	NC	NC

*Week 16 for the 20 mg/kg group males. Week 26 for 1 mg/kg and 5 mg/kg groups, and the 20 mg/kg group females. NC – Not calculated

Exposures to the active N-desmethyl AZD6244 metabolite were detectable in mice and generally higher in males than females (Table 9).

Table 9 26-Week Mouse Toxicokinetic of N-Desmethyl AZD6244

Dose Level (mg/kg, BID)	Sex	C _{max} (µg/mL)	T _{max} (h)	AUC _{0-12h}	AUC _{0-∞}	T _½
				µg•h/L	µg•h/L	
Week 1						
1	M	0.333	0.67	1.23	1.38	3.4
	F	0.125	0.67	0.497	0.646	5.6
5	M	1.12	0.67	4.02	4.37	2.9
	F	0.617	0.67	3.15	3.77	4.2
20	M	4.13	0.67	15.4	17.5	3.8
	F	3.29	0.67	10.4	12.7	5.1
Week 26/16*						
1	M	0.093	0.67	0.644	0.756	3.7
	F	0.123	0.67	0.537	0.733	6.4
5	M	0.524	0.67	2.76	3.88	6.7
	F	0.292	0.67	2.08	2.58	4.6
20	M	1.43	0.67	7.95	9.89	4.7
	F	0.706	0.67	4.07	NC	NC

Study Title/Number: 3-month Oral Toxicity Study in the Rat (528088)

Key Study Findings:

- Skin was considered to be the primary target organ for toxicity in rats in this study. Skin scabs and lesions in rats were associated with clinical observations and dose-dependent increases in incidence and severity of microscopic ulcerations in males ≥5 mg/kg/day and females at 2.5 mg/kg/day.
- In males dosed with 10 mg/kg BID selumetinib hyd-sulfate, physis dysplasia was observed in the femoro-tibial joint. Increased hematopoiesis in the femoral bone marrow in female rats at 12.5 mg/kg/day was not associated with peripheral hematology changes and was most likely a response to the skin lesions.

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- Soft tissue mineralization was observed in a number of tissues and was associated with changes in plasma inorganic phosphate and albumin.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Doses and frequency of dosing: Males: 0 (vehicle), 1, 2.5, 5, 10 or 20 mg/kg/day
Females: 0 (vehicle), 2.5, 5, 12.5, 25 or 50 mg/kg/day

Species/strain: Han Wistar CRL: WI(Han) rat
Number/sex/group: 10M and 10F
Route of administration: Oral (gavage)
Formulation/vehicle: 10% ethanol, 30% PEG 400 and 60% Phosal 50

Satellite groups: No - main study animals used for TK analysis
Study design: This study was performed to identify dose levels for a 2-year carcinogenicity study. The same vehicle as that intended for the 2-year carcinogenicity study was used in this study. Following early termination of animals in 20 (M), 25 (F) and 50 (F) mg/kg/day groups on Day 30, 2 additional groups, each consisting of 10M and 10F were included. Males were dosed at 1 or 2.5 mg/kg/day and females were dosed at 2.5 or 5 mg/kg/day for 3 months.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	Early termination of 2F at 50 mg/kg/day on Day 26 due to moribund conditions. Early termination of all males at 20 mg/kg/day and all surviving females at 50 and 25 mg/kg/day on Day 30 due to clinical signs.
Clinical Signs	Early decedents: skin lesions and/or scabs in the dorsal and abdominal regions; excessive grooming/scratching; ungroomed/erected fur; ploughing. Dose-dependent skin lesions and/or scabs in females at all dose levels and in males at ≥ 5 mg/kg/day. Sporadic incidences of salivation in males ≥ 2.5 mg/kg/day.

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Parameters	Major Findings
	Sporadic incidences of salivation, fur staining, red liquid, ploughing, and excessive grooming at all dose levels in both sexes
Body weight	↓ mean body weight in 50 mg/kg/day females (0.9x). No other selumetinib-related effects on body weights
Ophthalmology	No selumetinib-related changes.
Hematology	↑ neutrophils (up to 11.5x) and monocytes (up to 8.3x) associated with a concomitant ↑ in white blood cells in males at 20 mg/kg/day, 1M at 10 mg/kg/day, and females at 12.5, 25 and 50 mg/kg/day. ↑ platelets (up to 1.8x) in females ≥12.5 mg/kg/day. Minimal ↓ in red blood cell mass (0.91x) with associated ↑ in reticulocyte (1.2- to 1.5-fold) in females at ≥25 mg/kg/day.
Serum Chemistry	↑ AST: Week 4 - in males (1.2x) at 20 mg/kg/day and in females (1.5x) at ≥ 12.5 mg/kg/day; Week 13 - in males (1.2x) at 10 mg/kg/day and in females (1.4x) at 12.5 mg/kg/day. ↑ ALT: Week 4 - in females (1.5x) at ≥25 mg/kg/day. ↑ Phosphate levels: Week 4 - in males (1.2x) at 20 mg/kg/day and females (1.7x) at ≥25 mg/kg/day; Week 13 - in females (up to 1.5x) at ≥2.5 mg/kg/day. ↓ Albumin levels: Week 4 - in males at 20 mg/kg/day and females at ≥12.5 mg/kg/day (up to 0.65x); Week 13 - males at 10 mg/kg/day and females at ≥2.5 mg/kg/day. ↑ Globulin levels: Week 4 - in males at 20 mg/kg/day and females at ≥12.5mg/kg/day (up to 1.8x); Week 13 - males at 10 mg/kg/day and females at ≥2.5 mg/kg/day. Changes in the albumin and globulin resulted in ↓ total protein and A/G. ↓ Bile acid: Week 4 - in males at ≥2.5 mg/kg/day and females at ≥12.5 mg/kg/day.
Urine Analysis and Urine Chemistry	↑ urine protein/creatinine ratio: Week 4 – in females (2x) at 50 mg/kg/day.
Gross Pathology	Unscheduled termination: skin scabs; enlarged mandibular lymph nodes, and small thymus. Scheduled termination (Day 30 and Day 92/93): Skin scabs: in 1M at 5 mg/kg/day or 2M at 10 mg/kg/day and 7M at 20 mg/kg/day; 3F at 2.5 mg/kg/day; 8F at 5 mg/kg/day and all females at ≥12.5 mg/kg/day. Enlarged axillary and/or mandibular lymph nodes: a few males and females at ≥10/12.5 mg/kg/day.
Organ Weight	↑ adrenal weights in females at 12.5 mg/kg/day. ↑ kidney weights in females at 12.5 mg/kg/day. ↓ spleen weight in males at ≥5 mg/kg/day.
Histopathology	Unscheduled termination: Skin ulceration; ↓ cellularity of femoral bone marrow; mineralization of glandular mucosa of the stomach, kidney, heart, lymph node; ↓ cellularity in thymus and atrophy of uterus and vagina. Scheduled termination (Day 30 and Day 92/93): Skin ulceration: Dose dependent ↑ incidence and/or severity in males at ≥5 mg/kg/day and in females at ≥2.5 mg/kg/day. Femoral bone: physis dysplasia (minimal-mild) in males at ≥10 mg/kg/day. Femoral bone marrow: ↓ cellularity in females at ≥25 mg/kg/day; ↑ hematopoiesis in females at 12.5 or 25 mg/kg/day. Mineralization:

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Parameters	Major Findings
	- Stomach: males at ≥ 5 mg/kg/day and females at ≥ 25 mg/kg/day. - Kidney: males at ≥ 1 mg/kg/day and females at ≥ 2.5 mg/kg/day; vascular - males at ≥ 10 mg/kg/day and females at ≥ 25 mg/kg/day. - Heart: males at ≥ 10 mg/kg/day and 1 female at 25 mg/kg/day. - Aorta: males at 20 mg/kg/day and females at ≥ 25 mg/kg/day. - Mesenteric lymph node: females at 50 mg/kg/day and 1 female at 25 mg/kg/day. - Lung: males at 20 mg/kg/day. - Liver: 1 male at 1 mg/kg/day; males at ≥ 5 mg/kg/day and 1 female at 25 mg/kg/day. - Tongue: males at 20 mg/kg/day and 1 female at 25 mg/kg/day.

A/G Albumin:globulin; ALT Alanine aminotransferase; AST Aspartate aminotransferase; F Female; M Male.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

FDA Assessment: In general, FDA agrees with the Applicant's assessment of the rat toxicology data. The skin was the major target organ leading to early sacrifice of females at the highest dose levels. Increases in neutrophils and white blood cells may correlate with the increased incidence of skin lesions. Organ mineralization occurred in the kidneys even at the lowest dose levels. All animals given AZD6244 were exposed to AZD6244 and its metabolites, N-desmethyl AZD6244 and AZD6244 amide, though metabolite exposures in rats were extremely low. The pharmacokinetic data for AZD6244 is included here (Table 10).

Table 10 Toxicokinetic Data for AZD6244 in Rats

Dose level (mg/kg)	Males					
	Day 28			Week 13		
	C _{max} ($\mu\text{g/mL}$)	AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{h/mL}$)	T _{max} (h)	C _{max} ($\mu\text{g/mL}$)	AUC ₀₋₂₄ ($\mu\text{g}\cdot\text{h/mL}$)	T _{max} (h)
1	1.58	26.61	4	1.73	27.16	4
2.5	2.77	43.65	2	4.50	62.75	4
5	8.34	117.7	4	8.61	131.0	4
10	12.27	196.5	2	14.9	250.1	2
20	27.21	462.6	2	-	-	-
	Females					
2.5	7.70	88.39	4	7.51	86.10	4
5	12.69	186.9	2	15.07	186.0	2
12.5	25.05	302.3	4	20.11	245.9	1
25	24.82	369.1	2	-	-	-
50	45.80	755.7	4	-	-	-

Study Title/Study Number: 26-week Oral Toxicity Study in the Cynomolgus Monkey (VKS/0210)

Key Study Findings:

- Administration of selumetinib to monkeys for up to 26 weeks was associated with loose/liquid feces, seen at 1.5 mg/kg BID in females and 4 mg/kg BID in males. Diarrhea was occasionally associated with signs of dehydration and/or body weight loss.
- Selumetinib-related GI disturbances were not associated with any macroscopic or microscopic changes.
- The no-observed-adverse-effect-level (NOAEL) in males was considered to be 1.5 mg/kg BID, however, a NOAEL was not established in females due to the liquid feces and dehydration observed in one female on Week 18. The dose of 0.5 mg/kg BID was considered to be the NOEL.

Conducting laboratory and location:

[REDACTED] (b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing: 0 (vehicle), 0.5, 1.5 or 4 mg/kg BID (total doses of 1, 3, or 8 mg/kg/day); given approximately 12 hours apart

Route of administration: Oral (gavage)

Formulation/vehicle: 30% w/v aqueous Captisol

Species/strain: Cynomolgus monkey

Number/sex/group: 4M and 4F

Age: 33 to 44 months

Satellite groups/unique design: No

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major Findings
Mortality	None
Clinical Signs	Loose/liquid feces: in control and 0.5 mg/kg BID (sporadic), at 1.5 and 4 mg/kg BID and in females at 4 mg/kg BID (most prominent); occasional association with signs of dehydration and/or body weight loss requiring rehydration therapy (on occasions). Dosing holiday for 7 days (Weeks 18 to 19) for 1F at 4 mg/kg BID due to weight loss (10% loss overall) but dosing recommenced on Day 2 of Week 19. Dark feces with occult blood, and slight dehydration in Week 18 in 1F at 1.5 mg/kg BID that necessitated short dosing holiday (3.5 days) in Weeks 18 to 19.
Body Weight	Similar mean body weight gains for treated and concurrent control groups.
Ophthalmoscopy	No treatment-related ocular changes were noted.
ECG	No apparent treatment-related effects on ECG measurements.

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Parameters	Major Findings
Hematology	↓ mean hematocrit, hemoglobin, red blood cell count, and the associated mean cell hemoglobin and mean cell hemoglobin concentration in males at 4 mg/kg/day.
Clinical Chemistry	4 mg/kg BID: ↓ in plasma albumin and A/G ratio and ↑ mean beta and gamma globulins for both sexes; ↑ plasma AST, and ↓ cholesterol and calcium; ↑ plasma phosphorus in 1M. 1.5 mg/kg BID: ↑ in plasma phosphorus in males and ↓ A/G ratio for both sexes.

FDA Comment on Clinical Chemistry: In addition to the clinical changes described by the Applicant, there were changes in blood urea nitrogen and triglycerides. Increases in phosphorous were up to 26% at the high dose in monkeys.

Table 11 Additional Clinical Chemistry Changes in Monkeys

Parameter	Sex	0		0.5		1.5		4	
		(mg/kg) bid							
Week→		13	26	13	26	13	26	13	26
AST (IU/L)	M	35	28	--	--	--	↑96%	↑77%	↑114%
	F	42	39	--	--	--	--	--	↑136%
Phosphorus (mmol/L)	M	2.25	2.07	--	--	↑13%	↑20%	↑26%	↑22%
	F	2.15	1.89	--	--	--	--	--	↑14%
BUN (mmol/L)	M	4.42	3.70	↑30%	↑91%	↑52%	↑100%	--	↑77%
	F	5.46	5.03	↑17%	--	--	↓28%	--	--
Triglycerides (mmol/L)	M	0.33	0.39	↑39%	↑31%	↑79%	↑49%	↑76%	↑69%
	F	0.78	0.61	↓23%	--	↓29%	↓20%	↓26%	--

Gross Pathology	No lesions attributable to the treatment reported.
Organ Weight	No treatment-related changes reported.
Histopathology	No microscopic lesions attributable to treatment identified.
Other Evaluations	None

A/G Albumin:globulin; AST Aspartate aminotransferase; BID Twice daily; ECG Electrocardiogram; F Female; M Male.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment of general toxicology findings in monkeys. The increases in BUN, AST, and triglycerides suggest some potential for hepatotoxicity. Exposure (C_{max} and AUC) to AZD6244 in monkeys increased with increasing dose (

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Table 12). There were no differences in exposure between the males and females, so their data were combined. N-desmethyl AZD6244 levels were below quantification.

Table 12 Summary of Toxicokinetic Parameters for AZD6244 in Monkeys

Week	Parameter	0.5	1.5	4.0
		(mg/kg) BID		
1	C _{max} (µg/mL)	0.16	0.43	2.11
	T _{max} (h)	1.0	1.56	0.88
	T _½ (h)	5.09	5.72	5.94
	AUC _{0→12} (µg*h/mL)	0.62	1.37	5.22
26	C _{max} (µg/mL)	0.26	0.80	2.84
	T _{max} (h)	0.94	0.75	0.69
	T _½ (h)	7.20	5.66	0.01
	AUC _{0→12} (µg*h/mL)	0.91	2.56	8.43

General Toxicology; Additional Studies

1-month Oral Toxicity Study in the Mouse Followed by a Recovery Period (0355AM)

In the 1-month study, dosing of selumetinib hyd-sulfate to mice at a dose of 103 mg/kg BID (total daily dose of 206 mg/kg/day) was not tolerated and resulted in unscheduled termination of several males. As a result, the high dose (HD) was reduced to 69 mg/kg BID (total dose of 137 mg/kg/day) on Day 12 and all remaining animals at this dose survived to the scheduled termination. The cause of death in these males, dosed at 103 mg/kg BID, was associated with erosive and inflammatory findings in the GI tract. In surviving animals, dosing of selumetinib hyd-sulfate was associated with adverse clinical signs (≥ 34 mg/kg BID) and serum chemistry (increases in plasma calcium and inorganic phosphate, and a decrease in albumin) changes (69 mg/kg BID). Microscopic evaluation showed dose dependent mineralization in various tissues (cornea, kidney, liver, myocardium, and skeletal muscle) at ≥ 11 mg/kg BID and erosive and inflammatory changes in the GI tract at 69 mg/kg BID. Additional microscopic findings in the 103/69 mg/kg BID group included bone marrow hypocellularity, increased EMH in spleen, and inflammatory cell infiltration of portal area in the liver. At the end of the 4-week recovery period, similar histopathological findings were still present but at a reduced incidence and/or severity compared to main test animals.

Maximum Tolerated Dose and 28-day Oral Toxicity Study in the Cynomolgus Monkey Followed by a 28 Day Recovery Period (VKS/0153)

This study consisted of an initial maximum tolerated dose (MTD) phase followed by a 1-month repeat dose phase. In the MTD phase, selumetinib hyd-sulfate was administered BID (12 hours apart) by oral gavage (0.5 mL/kg per occasion) to 2 male and 2 female cynomolgus monkeys at the following dose levels: 0.92 mg/kg BID (Days 1 to 7), 3 mg/kg BID (Days 9 to 14), 7.5 mg/kg BID (Days 15 to 21) and 15 mg/kg BID (Days 22 to 35), which were equivalent to total doses of 2, 6, 15, or 30 mg/kg/day, respectively.

Administration of selumetinib hyd-sulfate in MTD study at 15 mg/kg BID (30 mg/kg/day total) was not tolerated and resulted in abdominal discomfort, persistent loose/liquid/red stained feces, red anal discharge, dehydration and bodyweight loss, hematological changes in all animals and early termination of 1 male for humane reasons.

For the 28-day repeat dose phase of the study, groups of 2 male and 2 female cynomolgus monkeys received selumetinib hyd-sulfate dose levels of 0, 1.5, 5 or 10 mg/kg BID (3, 10, and 20 mg/kg/day total dose). Recovery was assessed in a separate group at 5 mg/kg BID. The clinical signs observed after 14 days of dosing at 10 mg/kg BID indicated that this dose could not be tolerated for the remaining duration. Dosing in the HD group was stopped for 1 day and the dose level was reduced to 7.5 mg/kg BID (15 mg/kg/day total dose) from Day 16 to termination. Histopathological evaluation of tissues was only conducted in animals dosed for 1 month with 10/7.5 mg/kg BID selumetinib and concurrent controls.

The predominant clinical findings seen at doses of ≥ 5 mg/kg BID were loose feces, which progressed into liquid feces as treatment continued and at the HD level, was associated with signs of dehydration (i.e., slightly sunken eyes). Following reduction of the HD level from 10 to 7.5 mg/kg BID from Day 16, persistent loose/liquid feces, piloerection, ungroomed appearance was seen in some animals necessitating a brief cessation of treatment for some animals. Body weight and food consumption were unaffected, despite the severity of the diarrhea. Minimal changes in clinical pathology parameters were noted at ≥ 5 mg/kg BID. There were no histopathological changes associated with dosing selumetinib at 10/7.5 mg/kg BID for 28 days. There was evidence of recovery from the gastrointestinal (liquid feces) and clinical pathology findings following a 28-day recovery period in animals.

Dosing at 1.5 mg/kg BID did not produce any significant test article-related changes and was therefore considered to represent a NOAEL following oral administration for 1 month.

The Applicant's Position:

The main target organs of toxicity in the repeat dose studies with selumetinib were skin, bone, and GI tract. Soft tissue mineralization was noted in a number of organs in rodents and was associated with increases in the plasma total phosphate and/or calcium and a decrease in albumin. With the exception of the soft tissue mineralization, all findings, in the repeat dose studies in mice and monkeys, showed evidence of reversibility following a recovery period.

The FDA's Assessment:

FDA agrees with the Applicant's overall assessment. See FDA's comments after each chronic study for details. Findings in the one-month studies were similar to those in the chronic studies with no additional target organs identified.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Data:

Study Title/Number: Bacterial Reverse Mutation Assay (AA78NV.503.BTL)

Key Study Findings:

- Selumetinib was not mutagenic in the presence or absence of rat S9 at concentrations up to 5000 µg per plate.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP2 uvrA; up to 5000 ug/plate; ±S9.

Selumetinib showed no evidence of mutagenic potential in the *S. typhimurium* strains and *E. coli* strain WP2 uvrA, when tested under the conditions used in this assay, up to the limit concentration of 5000 µg per plate, with or without metabolic activation (±rat S9).

The FDA's Assessment:

FDA agrees that the genetic toxicology studies support that selumetinib is not mutagenic in the bacterial reverse mutation assay.

In Vitro Assays in Mammalian Cells

Data:

Study Title/Number: Mammalian Gene Mutation Test in Mouse Lymphoma L5178Y cells (AA78NV.704.BTL)

Key Study Findings:

- Selumetinib was not mutagenic in a mouse lymphoma L5178Y tk locus assay in the presence or absence of rat S9.

GLP compliance: Yes

Test system: Mouse lymphoma L5178Y; up to 150 ug/mL; ±S9

In a mouse lymphoma L5178Y tk locus assay, selumetinib free base showed no evidence of mutagenic potential, with or without metabolic activation (±rat S9), when tested up to concentrations limited by precipitation and/or toxicity (maximum concentration tested was 150 µg/mL).

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Data:

Study Title/Number: Micronucleus Test in Bone Marrow Cells of Mice (0416QM)

Key Study Findings:

- Following oral administration for 2 days, selumetinib induced micronuclei in the bone marrow of CD-1 mice at doses ≥ 121 mg/kg/day with a confirmed NOEL of 24 mg/kg/day.

GLP compliance: Yes

Test system: Male CD-1 mice; bone marrow micronuclei; 2 oral doses (24 hours apart) of 0, 24, 121 or 242 mg/kg/day.

In this study, selumetinib hyd-sulfate was investigated for its potential to induce micronucleated polychromatic erythrocytes (PCEs) in mouse bone marrow. Groups of 7 male CD-1 mice received 2 oral doses (10 mL/kg) of 24 hours apart of 0, 24, 121 or 242 mg/kg/day selumetinib hyd-sulfate. A separate group of 3 mice was given a single oral dose of the positive control, cyclophosphamide (65 mg/kg). The animals were killed 24 hours after the last dose and femoral bone marrow samples collected. For each animal, the number of the micronucleated PCEs was counted in 2000 immature erythrocytes. As an estimate of bone marrow toxicity, the ratio of immature erythrocytes to mature erythrocytes was determined in 1000 cells.

There was a significant increase in micronucleated PCEs in the bone marrow of mice at selumetinib doses of 121 or 242 mg/kg/day. A dose of 24 mg/kg/day did not induce an increase in micronuclei formation and was considered to be the NOEL. There was no evidence of bone marrow toxicity.

Other Genetic Toxicity Studies (For API only; does not refer to impurities)

Data:

Micronucleus Test in Bone Marrow Cells of Mice (0156QM)

In a GLP study, selumetinib free base given to groups of mice as single oral doses of 0, 500, 1000, and 2000 mg/kg produced a significant increase in micronuclei at 2000 mg/kg at 24 hours post dose. In a second study, selumetinib free base given to groups of mice as single oral doses of 0, 50, 160, 500, 1000, and 2000 mg/kg produced a biologically significant increase in micronucleated immature erythrocytes (MIE) at dose levels of 1000 mg/kg and above at 24 hours post dose. The results obtained following dosing of 500 mg/kg (1 positive and 1 negative for the induction of MIE) were equivocal. The NOEL for the induction of micronuclei in the bone marrow of mice is 160 mg/kg selumetinib free base.

Centromeric Labelling of Slides from the Mouse Micronucleus Test After a Single Oral Dose (0120KY)

In this non-GLP study, unstained slides from the mouse in vivo micronucleus study (0156QM) were fluorescently labelled with a mouse pan-centromeric DNA probe and examined for the presence or absence of a centromere signal. The presence of a centromere signal within a micronucleus indicates the presence of a whole chromosome, suggesting that the micronucleus had arisen via an aneugenic mechanism. The absence of a centromere signal within the micronucleus indicates a chromosome fragment, resulting from breakage.

In mice given 500 mg/kg of selumetinib, all of the induced micronuclei were centromere positive. At doses of 1000 and 2000 mg/kg, 59% and 61% respectively, of the micronuclei were centromere positive. This suggests that the majority of the micronuclei formed are a consequence of chromosome loss, consistent with an aneugenic mode of action.

It was concluded that the majority of the micronuclei induced in the bone marrow of mice given selumetinib contain centromeric signals and, therefore, that selumetinib has an aneugenic mode of action. The reduction in proportion of micronuclei containing centromeric material at the highest selumetinib doses is consistent with the hypothesis that aneugens induce other forms of chromosome aberrations at cytotoxic dose levels.

The Applicant's Position:

Selumetinib showed no evidence of genotoxicity in vitro in bacterial or mammalian cells, but induced micronuclei in the bone marrow of mice in vivo, primarily as a consequence of aneugenicity.

The FDA's Assessment:

FDA agrees with the Applicant's assessment; however, the aneugenic findings in the in vivo studies all occurred at doses that were higher than the clinical dose. In the study using the hyd-sulfate (current clinical formulation) form of selumetinib the Applicant did not include a toxicokinetic assessment. There were no findings in the study using the hyd-sulfate formulation of selumetinib at the dose of 24 mg/kg. In the 26-week general toxicology study in mice, the high dose of 20 mg/kg resulted in a C_{max} of 29.6 µg/mL in males, a concentration approximately 38 times the human C_{max} at the 25 mg/m² twice daily. In the genetic toxicology studies using the free-base formulation, C_{max} plateaued at doses greater than the low dose of 50 mg/kg. Aneugenic findings occurred at a dose resulting in C_{max} values that were 30-40x higher than the human dose, FDA did not consider selumetinib positive for genotoxicity for the purposes of recommendations on contraception.

5.5.3. Carcinogenicity

Data:

Study Title/Number: A 6-Month Carcinogenicity Study in CByB6F1 rasH2 Transgenic Mice (20086561)

Key Study Findings:

- Selumetinib at doses up to 15 mg/kg BID (30 mg/kg/day) was not carcinogenic in CByB6F1/Tg rasH2 hemizygous mice.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Doses and frequency of dosing:

0 (vehicle), 3, 8, 25/15 mg/kg BID (total dose 0, 6, 16, 50/30 mg/kg/day); BID approximately 12 hours apart

Basis for dose selection:

Dose selection based on an MTD and 7-day DRF study and a 1-month repeat dose study in CByB6F1 hybrid mice as well as repeat dose studies in CD-1 mice. The dose levels were approved by the FDA Carcinogenicity Assessment Committee.

Species/strain:

CByB6F1-Tg(HRAS)2Jic Hemizygous mouse

Age:

8 weeks

Number/sex/group:

25/sex/group

Route of administration:

Oral (gavage); the positive control group received N-nitrosomethylurea (NMU) by intraperitoneal (IP) route

Formulation/vehicle:

10% ethanol, 30% PEG 400, and 60% Phosal 50 PG

Satellite groups:

Selumetinib treated groups: 18 mice (non-transgenic littermates)/sex/group
Control groups: 12 mice (non-transgenic littermates)/sex/group

Control:

Deionized water and NMU; positive control)

Study design:

One group of Tg rasH2 mice consisting of 15 M and 15 F received 7.5 mg/mL NMU by IP. HD was reduced from 25 mg/kg BID to 15 mg/kg BID on Day 130 following a discussion with the FDA.

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Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	Main study: Mortality was considered low 1% in control (1 of 100; excluding NMU group) and 2.7% (4 of 150) in selumetinib treated groups. Early terminations due to clinical observations: 3M at 25 mg/kg BID and 1F at 8 mg/kg BID on Days 89 or 90. 3M (TK) and 1F (TK) at 25 mg/kg BID on Days 69, 82, 110 and 114, respectively. 4M (TK) at 8 mg/kg BID on Days 70, 78, 140, and 145.
Clinical Signs	Unscheduled mortality: ↓ activity, hunched posture, tremors and cold to touch, dehydration, and irregular respiratory rate. 1M and 2F at 25 mg/kg BID TK dose group placed on dosing holiday on Day 114 (Week 17), based on clinical observations and body weight loss. Remaining 25 mg/kg BID TK animals placed on dosing holiday on Day 116, based on notable body weight loss. No selumetinib-related observations in the surviving animals following dose reduction.
Body Weight	↓ Mean body weight gain for the 25/15 mg/kg BID (both sexes) from Days 134 to 182; ↓ mean body weight gain at 25/15 mg/kg BID in TK animals from Day 85 to 113; partial recovery in mean body weight gain demonstrated following a dosing holiday from Days 114 or 116 to 130 for TK animals.
Food Consumption	No apparent selumetinib-related effects.
Gross Pathology	No selumetinib-related gross pathology at unscheduled or scheduled necrosis.
Histopathology (Non-neoplastic)	Cecum: crypt hyperplasia (minimal-mild) at ≥8 mg/kg BID. Colon: crypt hyperplasia (minimal to moderate) in males at ≥3 mg/kg BID and females at 25/15 mg/kg BID. Colon: diverticulum (minimal-mild) in males and females at 25/15 mg/kg BID characterized by the presence of dilated crypts filled with basophilic fibrillary material; appeared to progress to thin wall structures lined by flattened cells, filled with basophilic fibrillary material, and surrounded by lymphocytes and plasma cells; found throughout the wall of the colon with extension into the serosa and mesentery and in association with crypt hyperplasia. Spleen: increased pigmented macrophages (minimal-mild) in males and females at ≥3 mg/kg BID.
Histopathology (Neoplastic)	No selumetinib-related neoplastic microscopic findings at any dose level
Positive Control (NMU)	High incidence of mortality in males (13 out of 15 [87%]) and females (12 out of 15 [80%]) were observed; expected neoplastic increases in the incidence of lymphoma, papilloma, and squamous cell carcinoma, and non-neoplastic (NMU-related retinal atrophy) microscopic changes were reported.

BID Twice daily; F Female; M Male; NMU N-nitrosomethylurea; TK Toxicokinetic.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

Study Title/Number: 2-Year Oral (Gavage) Carcinogenicity Study in Rat with Selumetinib hyd-sulfate (501094)

NDA Multi-disciplinary Review and Evaluation NDA 213756
Koselugo (selumetinib)

Key Study Findings:

- Selumetinib was not carcinogenic at doses up to 2.5 or 1 mg/kg/day in male and female Han Wistar rats, respectively.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Doses and frequency of dosing:

Males: 0 (vehicle), 0.25, 0.8, 2.5 mg/kg/day

Females: 0 (vehicle), 0.1, 0.3, 1 mg/kg/day

Once daily dosing

Basis for dose selection:

MTD and 14-day DRF and a 3-month repeat dose study

The dose levels were approved by the FDA Carcinogenicity Assessment Committee.

Species/strain:

Han Wistar CRL:WI(Han) rat

Number/sex/group:

50/sex/group

Age:

7-9 weeks old

Route of administration:

Oral (gavage)

Formulation/vehicle:

10% ethanol, 30% PEG 400 and 60% Phosal 50

Control:

Reverse osmosis deionized water

Satellite groups:

No-main study animals used for TK

Study design:

Three groups of Han Wistar rats received selumetinib orally, once daily for 2 years
Control group received either deionized water or vehicle

Deviation from study protocol affecting interpretation of results:

No

Observations and Results

Parameters	Major Findings
Mortality	No statistically significant differences (Kaplan-Meier) in mortality between any of the groups and the vehicle control for males or females.
Clinical Signs	Dose-dependent skin scabs and fur staining (yellow) in males and females at all dose levels.
Body Weight	No selumetinib-related effects.
Food Consumption	No selumetinib-related effects.
Ophthalmology	No selumetinib-related effects.
Hematology	↓ absolute and percentage reticulocyte count compared with controls at 2.5 mg/kg/day.
Gross Pathology	Mesenteric lymph node: ↑ incidence of dark discoloration in males at 2.5 mg/kg/day.

NDA Multi-disciplinary Review and Evaluation NDA 213756
Koselugo (selumetinib)

Parameters	Major Findings
Microscopic Pathology	Skin: erosion/ulceration ↑ incidence and/or severity in males at ≥0.8 mg/kg/day. Skin: erosion/ulceration with ↑ severity in females at 1 mg/kg/day. Mesenteric lymph node: ↑ incidence of erythrophagocytosis/erythrocytosis in males at 2.5 mg/kg/day.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

The Applicant's Position:

Selumetinib showed no evidence of carcinogenicity in 6-month CByB6F1/Tg rasH2 transgenic mouse and 2-year Han Wistar rat studies.

The FDA's Assessment:

After an independent review of the carcinogenicity studies including a statistical analysis of the findings, the results of the 6-month study in transgenic mice and the 2-year study in rats were presented to the Executive Carcinogenicity Assessment Committee. FDA's review of these data focused on the neoplastic findings. Exposures (AUC) in the carcinogenicity studies at the highest dose levels were at least 15 times higher than the clinical exposure at the 25 mg/m² twice daily dose even at the lowest tested doses in both species. The Committee agreed that the Applicant's studies were adequately conducted and showed no evidence of selumetinib-mediated carcinogenic potential.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Data:

Study Title/Number: 26-week Oral Toxicity Study in the Mouse with Assessment of Effects on Male Fertility Followed by a 13-week Recovery Period (VKS/0211)

Key Study Findings:

- Selumetinib at doses up to 20 mg/kg BID had no effect on male fertility in this study.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

0 (vehicle), 1, 5 and 20 mg/kg BID (total doses of 0, 2, 10, and 40 mg/kg/day); given BID approximately 12 hours apart

Route of administration:

Oral (gavage)

Formulation/vehicle:

30% Captisol in water

Species/strain:

CrI:CD1(ICR) mouse

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Version date: July 24, 2019 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Koselugo (selumetinib)

Number/sex/group: 20M in the low dose (LD) and mid dose (MD) groups; 25M in the control and HD groups. Undosed females were paired with study males on a 1:1 basis.

Satellite groups: 9/sex in control group and 18/sex in dosing groups

Study design: This study was designed to assess repeat dose toxicity in addition to male fertility. Only those parameters and assessments specific to male fertility are described here; for all other assessments, see Section 5.5.1. Following 10 weeks of treatment, treated males were paired with untreated females on a 1:1 basis. The day on which evidence of copulation was observed was considered to be Gestation Day (GD) 0. Undosed females were necropsied on GD 14 for evaluation of uterine content. Males receiving 20 mg/kg BID were necropsied during Week 16 of treatment. Main study males were necropsied after 26 weeks of treatment.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	Data presented for general toxicity endpoints above. See Section 5.5.1.
Clinical Signs	Data presented for general toxicity endpoints above. See Section 5.5.1.
Body Weight	Data presented for general toxicity endpoints above. See Section 5.5.1.
Mating Performance and Fertility	All animals mated within the first week of pairing. Fertility rates were 92%, 90%, 100%, and 92% for males receiving 0, 1, 5, or 20 mg/kg/day BID, respectively. No effect on pre or post implantation loss, or numbers of live embryos.
Necropsy Findings	Data presented for general toxicity endpoints above. See Section 5.5.1. Data for sperm motility and counts only presented here. LD: None MD: None HD: Not assessed; animals terminated prematurely.

BID Twice daily; HD High dose; LD Low dose; MD Mid dose.

Study Title/Number: Fertility and Early Embryonic Development Study in the Female Mouse with an Assessment of Recovery (0496GM)

Key Study Findings:

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Koselugo (selumetinib)

- Selumetinib had no effect on fertility in female mice at dose levels (≥ 12.5 mg/kg BID) that resulted in minimal maternal toxicity. Although mating performance and fertility were not affected, the number of live fetuses was slightly reduced; no effects were apparent on any parameter after 3 weeks treatment withdrawal.
- The NOAEL for both maternal toxicity and effects on reproductive performance was considered to be 2.5 mg/kg BID (total dose 5 mg/kg/day).

Conducting laboratory and location: AstraZeneca R&D, Macclesfield, UK
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (vehicle), 2.5, 12.5 and 37.5 mg/kg BID (total doses of 0, 5, 25, and 75 mg/kg/day); given BID approximately 12 hours apart.

Route of administration: Oral (gavage)

Formulation/vehicle: 30% Captisol in water

Species/strain: Alpk: APfCD-1 mouse

Number/sex/group: 22 females/group; 12 females in the HD and control group for recovery assessment.

Satellite groups: No

Study design: Female mice were dosed for 14 days prior to and during pairing, and for up to GD 6; recovery animals were dosed for 21 days and then left for a 21-day non-dosing period prior to pairing.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major Findings
Mortality	None attributable to treatment.
Clinical Signs	Slight patchy hair loss at ≥ 12.5 mg/kg BID.
Body Weight	↓ Pre-pairing body weights in main test animals at ≥ 12.5 mg/kg BID; Transient body weight losses between Days 3 and 4 and Days 9 and 10 in the main 37.5 mg/kg BID group. No treatment-related body weight losses for recovery animals (37.5 mg/kg BID) during the pre-pairing dosing or recovery periods.
Reproductive Performance	The pre-coital interval, mating and fertility indices in the selumetinib - treated (main and recovery) groups and control group were similar.
Necropsy findings	2.5 mg/kg BID: None 12.5 mg/kg BID: None 37.5 mg/kg BID: Liver discoloration in 3 main and 3 recovery females

NDA Multi-disciplinary Review and Evaluation NDA 213756
Koselugo (selumetinib)

Parameters	Major Findings
Uterine Examination	↓ in the number of live embryos at ≥12.5 mg/kg BID in the main test animals. This observation was not dose responsive. No differences in post implantation loss in main test groups when compared to the control group. No selumetinib-related effects on post-implantation loss or embryonic survival following a 21-day recovery period.

BID Twice daily.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

The Applicant's Position:

Selumetinib had no effect on fertility in male or female mice. Although mating performance and fertility were not affected, the number of live fetuses was slightly reduced; no effects were apparent on any parameter after 3 weeks treatment withdrawal.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The reduction in live fetuses in female mice treated with selumetinib was a reduction of a single fetus at each dose level other than control. There was also the loss of a single pup in the recovery cohort of dams treated 21 days prior to mating at the 37.5 mg/kg dose level. As the losses were of low incidence and not dose-dependent, the data does not suggest a selumetinib-mediated decrease in female fertility.

The Applicant conducted the male fertility assessment as a part of the 26-week general toxicology study in mice. While there were pre- or post-implantation losses in naïve female mice mated to male mice treated with selumetinib for 10 weeks, these losses did not exceed losses that occurred in females mated to control males and there no clear effects on fertility. Repeated treatment of male mice with AZD6244 at doses up to 5 mg/kg BID (~1.4 times the clinical exposure at 25 mg/m² BID) for 26 weeks had no adverse effects on progressive motility or sperm numbers. The Applicant could not perform sperm analysis on males at the 20 mg/kg dose level due to the premature sacrifice of these animals by Week 16.

Embryo-Fetal Development

Data:

Study Title/Number: Dose Range Finding Embryofetal Development Study in the Mouse (0430RM)

A dose-range finding embryofetal development (EFD) study in mated female CD-1 mice (10/group) was conducted to establish dose levels for a pivotal EFD study. Selumetinib was given to mice by oral gavage at 0, 2.5, 12.5, 37.5, or 75 mg/kg BID (total doses of 0, 5, 25, 75, or 150 mg/kg/day) during the period of organogenesis (Days 6 to 16 of post coitum). Selumetinib dosing up to 75 mg/kg BID was well tolerated with no evidence of maternal toxicity but caused embryo lethality, reductions in mean fetal weights, fetal malformations including open eye,

incomplete closure of the abdominal wall and/or cleft palate at ≥ 12.5 mg/kg BID. The NOEL for embryo-fetal survival and development in this study was 2.5 mg/kg BID.

Study Title/Number: Embryofetal Development Study in the Mouse (0480TM)

Key Study Findings:

- Administration of selumetinib to female mice during the period of major embryonic organogenesis resulted in open eye in all fetuses and an increased incidence of cleft palate of dams dosed with 37.5 mg/kg BID selumetinib.
- Open eye was observed in a number of fetuses from the 2.5 mg/kg BID and was considered to be associated with erroneous administration of 37.5 mg/kg BID on Day 16 post-coitum in the respective animals.
- The NOAEL for maternal toxicity and fetal abnormalities and variants was considered to be 2.5 mg/kg BID (unbound $AUC_{(0-12)}$ of 113.8 ng.h/mL; Study 0430RM). The animal-to-human AUC ratio for EFD findings for the recommended human dose of 25 mg/m² is >3.5 . To provide the most conservative safety margins, the unbound AUC value was used in the calculation.

Conducting laboratory and location: AstratraZeneca R&D, England
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 2.5 and 37.5 mg/kg BID (0, 5, and 75 mg/kg/day total dose level); given BID approximately 12 hours apart

Route of administration: Oral (gavage)

Formulation/vehicle: 30% w/v aqueous Captisol

Species/strain: Alpk: APfCD-1 mouse

Number/sex/group: 22 mated females/group

Satellite groups: No-TK evaluation conducted in the DRF study (0430RM)

Study design: Time mated female mice were dosed from GD 6 to GD 16, encompassing the period of major embryonic organogenesis

Deviation from study protocol affecting interpretation of results: During the study an administration error occurred and 9 females in the 2.5 mg/kg BID group received the 37.5 mg/kg formulation at their first daily dose administration occasion. Three of these females had fetuses with open eyes within their litter. Each of the affected dams received the increased dose on Day 16 post-coitum which corresponds with period

eyelid closure in mice (Day 15.5-16.5 post-coitum). None of the 12 correctly dosed females or the 5 incorrectly dosed females which were outside the window of sensitivity had fetuses with open eyelids.

Observations and Results

Parameters	Major Findings
Mortality	None
Clinical Signs	No treatment-related adverse effects recorded.
Body Weight	↓ Maternal body weight gain (4% - 6%) at 37.5 mg/kg BID from Day 11 to scheduled termination on GD 18. Slight ↓ in maternal food consumption at 37.5 mg/kg BID from GD 12 to GD 18. ↓ Gravid uterus weight at 37.5 mg/kg BID.
Necropsy Findings Cesarean Section Data	2.5 mg/kg BID: None 37.5 mg/kg BID: ↓ number of live fetuses; ↑ in post implantation loss, both in terms of early and late intrauterine deaths.
Necropsy Findings Fetal/Offspring	2.5 mg/kg BID: No effect on litter or fetal weights; uni- or bilateral open eye in a total of 10 fetuses from 3 dams. Each of the affected dams received the high dose (37.5 mg/kg by error) on GD 16 which corresponds with period eyelid closure in mice (Day 15.5 to Day 16.5 post-coitum). 37.5 mg/kg BID: ↓ Mean litter weights and mean fetal weight. Bilateral open eye in all fetuses; Cleft palate ; ↑ incidence of folded retina and changes to the consistency of the lens in the eyes in a number of fetuses.

BID Twice daily; GD Gestation Day.

↓: indicates reduction in parameters compared to control.

↑: indicates increase in parameters compared to control.

The Applicant's Position:

Given the demonstrated potential for embryo-fetal toxicity and fetal abnormalities with selumetinib in mice at clinically relevant plasma exposure, and the known fetal developmental abnormalities seen in nonclinical studies with other approved MEK inhibitors, a second EFD study in a non-rodent species was considered not to provide additional information which could enhance the risk assessment in patients. Based on the nonclinical data, administration of selumetinib can cause embryofetal toxicity and therefore appropriate measures should be implemented to avoid the risk to the developing fetus, in conjunction with applicable risk-benefit considerations.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that the embryo-fetal development studies in rats were sufficient to demonstrate risks to a developing fetus. In general, while FDA does calculate free C_{max} values for comparisons to in vitro IC₅₀ data in pharmacology studies, FDA does not

calculate unbound vs. bound C_{max} and AUC values for exposure comparison to humans for drugs with similar levels of protein binding in humans vs. animals, resulting in slight discrepancies in exposure margins between the Applicant and the FDA. The dose-range finding study for selumetinib in pregnant mice included two additional dose levels compared to the GLP-compliant study: 12.5 and 75 mg/kg twice daily. At the 12.5 mg/kg twice daily dose level the selumetinib exposure in dams was approximately 33 times the human exposure at the 25 mg/m² twice daily dose. Findings at the 12.5 mg/kg dose level included increased post-implantation loss and cleft palate; open eyes occurred in fetuses from all litters at this dose level. While the Applicant attributes the open eye incidence at the dose of 2.5 mg/kg in Study #0480TM to dosing error (the dams having been administered a higher dose), in the pre- and postnatal development study (Study 20082140), there were findings of prematurely open eyes at all dose levels, including the low dose of 0.5 mg/kg (~0.6 times the human exposure at the 25 mg/m² twice daily clinical dose), suggesting that defects in eyelids may occur at even lower doses.

Prenatal and Postnatal Development

Data:

Study Title/Number: Perinatal and Postnatal Development Study in the Mouse (20082138)

A dose-range finding pre and postnatal development (PPND) study was conducted in time mated female CD-1 mice (8/group) to establish dose levels for a pivotal PPND study. Selumetinib was given to mice by oral gavage at 0, 5, 12.5, 25, 40, or 75 mg/kg BID (total doses of 0, 10, 25, 50, 80, or 150 mg/kg/day) on GD 6 to Lactation Day 15. Another group were dosed at 75 mg/kg BID (150 mg/kg/day) from GD 15 to Lactation Day 15. Surviving F0 generation female mice and their litters were killed on Lactation Day 15. Administration of selumetinib at ≥40 mg/kg BID was associated with clinical signs (including piloerection, hunched posture and tremors) animals which exhibited clinical signs did not deliver a litter. Lower maternal body weight gain was observed at ≥5 mg/kg BID. Embryofetal death including total litter loss occurred resulting in low gestation index at 25 and 40 mg/kg BID (dosed from GD 6) and 75 mg/kg BID (dosed from GD 16), no live offspring were born in the 75 mg/kg BID (dosed from GD6). Decreased offspring viability was noted at ≥25 mg/kg BID. Decreases in pup weight were noted at ≥12.5 mg/kg BID. Selumetinib-related adverse clinical signs noted in the F1 generation pups during the postpartum period were generally associated with the decreased viability at ≥12.5 mg/kg BID. Other changes observed in the offspring attributed to selumetinib included lenticular opacities, open eyes, cleft palate or inward rotation of the hindlimbs at ≥12.5 mg/kg BID.

Study Title/Number: Perinatal and Postnatal Development Study in the Mouse (20082140)

Key Study Findings:

- There were no selumetinib related effects on maternal reproductive function, and the reproductive NOAEL is considered to be 7.5 mg/kg BID (total dose of 15 mg/kg/day).
- A developmental NOAEL could not be established based on the low incidence of open eyes noted at the lowest selumetinib dose of 0.5 mg/kg BID (1 mg/kg/day).
- Malformations occurred at a mean maternal plasma concentration (unbound C_{max}) 0.4-fold the clinical exposure at the recommended clinical dose of 25 mg/m². To provide the most conservative safety margin, the mean unbound C_{max} was used in this calculation.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

0 (vehicle), 0.5, 2, or 7.5 mg/kg BID (0, 1, 4, 15 mg/kg/day); given BID approximately 12 hours apart

Route of administration:

Oral (gavage)

Formulation/vehicle:

10% ethanol, 30% PEG 400, and 60% Phosal 50 PG

Species/Strain:

CrI: CD1(ICR) mouse

Number/sex/group:

25 females/group

Satellite groups:

No

Study design:

F0 generation mice were dosed on GD 6 through Lactation Day 20 (mice that delivered a litter) or GD 22 (mice that did not deliver a litter). F1 generation pups were not directly given the test item or the control item formulations but may have been exposed in utero exposure or via maternal milk during the lactation period. On postnatal Day (PND) 4, F1 litters were reduced to 8 pups/litter. On PND 21, F1 pups were weaned and the F0 generation females were killed. On at least PND 90, mice were paired within each dose group (1:1 male to female, non-siblings). Surviving F1 generation male mice were killed after the completion of the cohabitation period (PND 113 to 123) and F1 generation female mice were killed on GD 13. Blood samples were collected from 5 dams/dose group and their litters on Day 4 of lactation for exposure evaluation.

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Generation	Major Findings
F0 Dams	One F0 generation female in the 0.5 mg/kg BID dose group was euthanized on Lactation Day 9 due to adverse clinical signs (hunched posture, body weight loss). The cause of death could not be established but was considered unrelated to selumetinib as it occurred in the low dose group. In addition, one F0 generation female in the 2 mg/kg BID was euthanized on Lactation Day 12 due to a suspected gavage error. There were no adverse maternal clinical signs or effects on maternal body weights in F0 generation females. No noteworthy findings were reported on natural delivery parameters or litter observations. There were no selumetinib-related maternal macroscopic findings at any dose level.
F1 Generation	Decreases in preweaning pup weight were noted at 7.5 mg/kg BID from PND 7 (up to 92% of controls). Body weights remained lower in the F1 generation animals during the post-weaning period. At termination, decreases in the absolute weight of the paired epididymides and absolute and relative weights of the paired testes noted at 7.5 mg/kg BID and were considered to be secondary to the reduced terminal body weights. A selumetinib-related increase in prematurely open eyes was observed at all dose levels (2, 4, and 13 pups from 1, 2, and 6 litters in 0.5, 2, and 7.5 mg/kg BID dose groups, respectively). A low incidence of cleft palate was observed at 2 and 7.5 mg/kg BID (1 and 2 pups each from a single litter/dose level, respectively). Similar findings (open eyes) were noted during the first day of the reflex and physical development evaluations (PND 13). At the 7.5 mg/kg BID dose level, there was a decrease in the number of pups that met the criterion for pupil constriction on PND 21.

BID Twice daily; PND Postnatal day.

The Applicant's Position:

The peri- and postnatal development toxicity studies demonstrated the potential for selumetinib to adversely affect embryofetal survival and development if administered to patients that are pregnant or breast feeding. Therefore, appropriate measures should be in place to avoid risk to developing fetus or breast-fed children.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. FDA has included Table 13 and Table 14 showing the concentration of AZD6244 in dams (F0 generation) and pups (F1 generation). Prematurely open eyes were present even in pups from dams treated with 0.5 mg/kg AZD6244 where exposure after 2 hours was about 0.6x clinical exposure. The inclusion of pharmacokinetic data in pups also shows that there was transfer of selumetinib in milk.

Table 13 Plasma Concentration ($\mu\text{g/mL}$) of AZD6244 and DesmethylAZD6244 in Pregnant Mice on Day 4 of Lactation

DAMS (F0)					
Dose (BID)		AZD6244		N-Desmethyl AZD62444	
mg/kg	mg/m ²	0 (Pre-dose)	2 h	0 (Pre-dose)	2 h
0.5	1.5	--	0.453 (0.59x)	--	0.146
2.0	6.0	--	1.15 (1.5x)	0.10	0.403
7.5	22.5	0.073 (0.09x)	4.18 (5.4x)	0.064	1.49

Numbers in parenthesis are fold plasma concentrations of AZD6244 in mice compared to humans (mouse/human) at the 25 mg/m² BID dose.

Table 14 Plasma Concentration ($\mu\text{g/mL}$) of AZD6244 and N-Desmethyl AZD6244 in Pups on Day 4 Postpartum

PUPS (F1)					
Dose (BID)		AZD6244		N-Desmethyl AZD62444	
mg/kg	mg/m ²	0 (Pre-dose)	2 h	0 (Pre-dose)	2 h
0.5	1.5	--	--	0.007	0.007
2.0	6.0	0.071 (0.09x)	0.072 (0.09x)	0.029	0.031
7.5	22.5	0.328 (0.43x)	0.355 (0.46x)	0.128	0.117

Numbers in parenthesis are fold plasma concentrations of AZD6244 in mice compared to humans (mouse/human) at the 25 mg/m² BID dose.

5.5.5. Other Toxicology Studies

Data:

Genotoxicity Studies with Metabolite:

- N-desmethyl selumetinib, a pharmacologically active but minor metabolite, was not mutagenic in the presence or absence of metabolic activation system ($\pm$ rat S9).

Bacterial Reverse Mutation Test (0750BV)

N-desmethyl selumetinib showed no evidence of mutagenic potential in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA, when tested at concentrations up to 5000 μg per plate, in the presence or absence of rat liver derived metabolic activation system ($\pm$ rat S9).

Mouse Lymphoma Assay (0751MV)

In a mouse lymphoma L5178Y tk locus assay, N-desmethyl selumetinib showed no evidence of mutagenic potential, in the presence or absence of metabolic activation ($\pm$ rat S9), when tested up to concentrations determined by toxicity and/or solubility in tissue culture medium (maximum concentration tested was 167 $\mu\text{g}/\text{mL}$).

Phototoxicity

- Selumetinib did not demonstrate a risk for phototoxicity at the highest recommended concentration of 100 $\mu\text{g}/\text{mL}$.

Selumetinib absorbs light in the ultraviolet (UV) range and showed enhanced cytotoxicity in the presence of UV light, in an in vitro 3T3 neutral red uptake phototoxicity test at 316 and 1000 $\mu\text{g}/\text{mL}$ concentrations which are 3- and 10-fold above the current International Conference on Harmonization (ICH) S10 2013 recommended maximum concentration of 100 $\mu\text{g}/\text{mL}$. The positive phototoxicity result was seen at concentrations significantly greater ($>8000\times$) than the free clinical C_{max} achieved at the maximum intended clinical dose of 25 mg/m^2 BID. The concentrations for the in vitro phototoxicity evaluation with selumetinib were selected based on the OECD 2004 432 evaluation criteria which was subsequently reduced from 1000 to 100 $\mu\text{g}/\text{mL}$ due to a high percentage of positive results. Additionally, selumetinib demonstrated low binding affinity for melanin in rat whole body autoradiograph. Therefore, selumetinib is not considered to demonstrate a risk for phototoxicity based on the available nonclinical information.

The FDA's Assessment:

While selumetinib did demonstrate a clear phototoxic potential at concentrations $\geq 316 \mu\text{g}/\text{mL}$, FDA agrees that considering the updated advice under ICH S10 (2015) regarding maximum concentrations for testing (100 $\mu\text{g}/\text{mL}$) and that the IC_{50} for neutral red uptake in the presence of selumetinib in the presence of irradiation was $> 100 \mu\text{g}/\text{mL}$, that selumetinib did not demonstrate clear phototoxic potential at clinically relevant concentrations.

Applicant's Position:

Overall, the nonclinical toxicology profile of selumetinib is considered to be acceptable for the proposed indication.

The FDA's Assessment:

FDA agrees that no additional nonclinical studies are warranted to support the use of selumetinib in the proposed patient population.

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Koselugo (selumetinib)

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Selumetinib is an inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinases 1 and 2 (MEK1/2) for the treatment of pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN). The proposed dosing regimen is 25 mg/m² orally twice daily (BID) on an empty stomach (fasted 2 hours before and 1 hour after each dose).

The Clinical Pharmacology section of the NDA is supported by single and multiple dose pharmacokinetics (PK) characterization, population PK and exposure-response analyses, absolute and relative bioavailability (BA), mass balance, food effect, hepatic impairment, renal impairment, race/ethnicity, QT, drug-drug interaction in vivo studies, in vitro studies, and physiologically-based PK (PBPK) modeling.

The proposed dosing regimen of 25 mg/m² BID is acceptable from a clinical pharmacology perspective. The key review questions focused on the appropriateness of the proposed dosing regimen in patients with body surface area (BSA) 0.55 - 0.69 m², dose recommendations for patients with moderate (b) (4) hepatic impairment and those requiring coadministration of strong and moderate CYP3A4 modulators, and administration with regards to food to potentially alleviate gastrointestinal toxicities.

Recommendations

This NDA is approvable from a clinical pharmacology perspective, provided the Applicant and the FDA reach an agreement regarding the labeling language. The key review issues with specific recommendations/comments are summarized below.

Review Issues	Recommendations and Comments
Pivotal evidence of effectiveness	An open-label, single arm trial (SPRINT Phase 2 Stratum 1) of selumetinib in pediatric patients with NF1 who have symptomatic inoperable PN provided primary evidence of effectiveness.
General Dosing instructions	The recommended dosage of selumetinib is 25 mg/m ² orally twice daily without food; minimum BSA of 0.55 m ² and capped at 50 mg when BSA is ≥1.9 m ² .

	Doses should be rounded to nearest achievable dose with 10 and 25 mg strength capsules.																																																			
	Body surface area	Dose in mg (twice daily)		Daily Dose level (mg/m²)																																																
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	≥1.90 m ²	50		<52.6																																																
Dosing in patient subgroups (intrinsic and extrinsic factors)	- Avoid coadministration of strong or moderate CYP3A4 inhibitors or fluconazole (strong CYP2C19 inhibitor/moderate CYP3A4 inhibitor). If coadministration of these medications is unavoidable, reduce starting dose as follows: - If patient is currently taking 25 mg/m² BID, dose reduce to 20 mg/m² BID - If patient is currently taking 20 mg/m² BID, dose reduce to 15 mg/m² BID																																																			
	<table border="1"> <thead> <tr> <th rowspan="2">Body Surface Area</th> <th colspan="2">If the current dosage is 25 mg/m² twice daily, reduce to 20 mg/m² twice daily (mg/dose)</th> <th colspan="2">If the current dosage is 20 mg/m² twice daily, reduce to 15 mg/m² twice daily (mg/dose)</th> </tr> <tr> <th>Morning</th> <th>Evening</th> <th>Morning</th> <th>Evening</th> </tr> </thead> <tbody> <tr> <td>0.55 – 0.69 m²</td> <td>10</td> <td>10</td> <td colspan="2">10 mg once a day</td> </tr> <tr> <td>0.70 – 0.89 m²</td> <td>20</td> <td>10</td> <td>10</td> <td>10</td> </tr> <tr> <td>0.90 – 1.09 m²</td> <td>20</td> <td>20</td> <td>20</td> <td>10</td> </tr> <tr> <td>1.10 – 1.29 m²</td> <td>25</td> <td>25</td> <td>25</td> <td>10</td> </tr> <tr> <td>1.30 – 1.49 m²</td> <td>30</td> <td>25</td> <td>25</td> <td>20</td> </tr> <tr> <td>1.50 – 1.69 m²</td> <td>35</td> <td>30</td> <td>25</td> <td>25</td> </tr> <tr> <td>1.70 – 1.89 m²</td> <td>35</td> <td>35</td> <td>30</td> <td>25</td> </tr> <tr> <td>≥ 1.90 m²</td> <td>40</td> <td>40</td> <td>30</td> <td>30</td> </tr> </tbody> </table>	Body Surface Area	If the current dosage is 25 mg/m ² twice daily, reduce to 20 mg/m ² twice daily (mg/dose)		If the current dosage is 20 mg/m ² twice daily, reduce to 15 mg/m ² twice daily (mg/dose)		Morning	Evening	Morning	Evening	0.55 – 0.69 m ²	10	10	10 mg once a day		0.70 – 0.89 m ²	20	10	10	10	0.90 – 1.09 m ²	20	20	20	10	1.10 – 1.29 m ²	25	25	25	10	1.30 – 1.49 m ²	30	25	25	20	1.50 – 1.69 m ²	35	30	25	25	1.70 – 1.89 m ²	35	35	30	25	≥ 1.90 m ²	40	40	30	30	- Avoid concomitant use with strong or moderate CYP3A4 inducers. - The recommended dosage for use in patients with severe hepatic impairment (Child Pugh C) has not been established. Reduce dose to 20 mg/m² in patients with moderate hepatic impairment (Child-Pugh B). No dose adjustment is recommended for patients with mild hepatic impairment. - No dose adjustment is recommended for patients with mild to severe renal impairment and patients with ESRD.	
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	No dose adjustment is recommended based on race (White, Asian, Black) or sex.
Labeling	The labeling reflects dosing recommendations for hepatic impairment, drug-drug interaction (DDI), and patients with BSA 0.55-0.69 m ² . The review team also had content and formatting change recommendations according to the guidance of clinical pharmacology section of labeling for human prescription drug and biological products - content and format (published December 2016).
Bridge between the to-be-marketed and clinical trial formulations	Free base suspension, hydra-sulfate capsule, and granule formulations were evaluated in the clinical development program of selumetinib. In this NDA submission, the to-be-marketed formulation, i.e., hydra-sulfate capsule, was used for relevant clinical pharmacology studies and for clinical studies in the pediatric patient population. Relative bioavailability studies provided adequate PK bridging between the formulations and the to-be-marketed formulation.

The following postmarketing requirement (PMR) is issued to the Applicant to study the PK and safety of selumetinib administered with food in pediatric patients:

- Submit the final report and datasets from a pharmacokinetic trial in pediatric patients to confirm the effect of a low-fat meal on selumetinib exposure with the marketed capsule formulation and evaluate whether administration of selumetinib with food may alleviate gastrointestinal toxicities. Confirm appropriate dosing recommendation of selumetinib with a low-fat meal that maintains efficacy with acceptable safety.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The clinical pharmacology of selumetinib has been well characterized in adult subjects, adult oncology patients and pediatric patients.

The PK of selumetinib in pediatric patients (aged 3 to 18 years old at initiation/enrollment) with NF1 and inoperable PN have been characterized following single and multiple dosing based on body surface area (BSA). There has been an extensive clinical pharmacology program (mass balance, food effect, hepatic and renal impairment, drug-drug interaction [DDI] studies with CYP3A4 strong inhibitor and inducer and CYP2C19 inhibitor, and ethnicity) as well as population PK analysis to characterize the PK of selumetinib in adults and pediatric patients which support

the proposed posology in pediatric patients and appropriate dosing recommendations. Furthermore, PK data from healthy subjects after single dosing, and in adult oncology patients with advanced solid malignancy after both single and multiple doses of selumetinib and the outcomes of the exposure efficacy and exposure safety analysis conducted in NF1 pediatric patients was used to support the recommended dose of 25 mg/m² selumetinib, administered orally BID on a continuous schedule.

Pharmacological activity is primarily due to selumetinib and although 2 metabolites of selumetinib were identified to have pharmacological activity, the N desmethyl metabolite is ~3 to 5 fold more potent than parent (circulates at 5% to 7% of parent) and may contribute to some activity while the amide metabolite is ~50-fold less potent in vitro (circulates at ~2% of parent) and is unlikely to do so.

The Applicant's Position:

The clinical pharmacology studies support the recommended dose of 25 mg/m² selumetinib, administered orally BID on a continuous schedule for the treatment of pediatric patients with NF1 and inoperable PN. The PK of selumetinib is similar in adult subjects, adult patients and pediatric patients allowing for the use of results from adult populations for dose guidance in pediatric populations.

The FDA's Assessment:

The FDA generally agrees with the Applicant's characterization of selumetinib PK in pediatric patients. The PK of selumetinib appears to be similar in adult and pediatric patients.

The FDA recommends a lower age cutoff i.e., 2 years of age and older for pediatric patients with NF1 and inoperable PN. Based on in vitro studies, selumetinib is primarily metabolized by CYP enzymes (56%, mainly by CYP3A4) with a lesser contribution by UGT enzymes (29%, UGT1A1 and UGT1A3), all of which have greater than 80% adult enzyme activity/maturation by 2 years of age.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The Phase I portion of the SPRINT study initially evaluated 2 doses of selumetinib, 20 and 30 mg/m² in pediatric patients with NF1 and inoperable PN to identify a suitable dose for Phase II. Initially, the lower dose of 20 mg/m² was considered appropriate for long term treatment, however after systematic review of emerging evidence from another study (Banerjee et al 2017; Pediatric Brain Tumor Consortium study which evaluated 25, 33 and 43 mg/m² BID; 25 mg/m² was selected as the recommended Phase II dose in that study as

33 and 43 mg/m² were not tolerated), an intermediate dose of 25 mg/m² was introduced into the SPRINT Phase I study which was determined to be safe and tolerable with potential for better efficacy and hence, was selected as the Phase II dose. This 25 mg/m² was defined as the MTD in both the SPRINT and Pediatric Brain Tumor Consortium pediatric studies.

The results of the exposure-response analysis for both efficacy and safety did not indicate a clear relationship between selumetinib exposure and response within the exposure range investigated in the SPRINT study. Using the primary NCI central analysis, no exposure-efficacy relationship was observed, although a slight trend towards a higher exposure leading to higher efficacy in the independent central reviewer analysis was noted. The median concentrations of responding patients were marginally higher than non-responders, although there was significant overlap in individual concentrations between patients in both groups. This suggests that higher exposures might be more beneficial, however an increase in dose to 30 mg/m² is not appropriate based on the long-term safety data from the SPRINT Phase I study (2/6 patients had DLT at 30 mg/m² dose; numerically more adverse events (AEs) at this dose group compared to 20 and 25 mg/m² dose). Importantly, the 25 mg/m² dose ensures that patients will receive a clinically active dose regardless of inter-patient variability and allows prescribers to reduce the dose should this be necessary.

The Applicant's Position:

Selumetinib dose of 25 mg/m² BID was identified as the recommended dose based on a review of all available safety, tolerability, pharmacokinetic, and efficacy data in the Phase I component of the SPRINT study. The exposure-response analyses confirmed a lack of relationship between selumetinib exposure and various efficacy or safety endpoints in the SPRINT study, indicating that the 25 mg/m² BID regimen produced robust and consistent therapeutic effects across the exposure range observed.

The FDA's Assessment:

The FDA agrees with the Applicant's proposed dosing regimen of selumetinib 25 mg/m² BID, which is supported by safety, and efficacy findings in the indicated patient population, and PK-PD relationships in pediatric and adult patients:

- (1) In SPRINT Phase I study, 25 mg/m² BID was determined to be the MTD and selected as the RP2D based on the following:
 - a. ORR was similar across 20 to 30 mg/m² BID doses with best ORR observed at 25 mg/m² BID, i.e., 66.7% (8/12) at 20 mg/m², 83.3% (5/6) at 25 mg/m², 50.0% (3/6) at 30 mg/m².
 - b. Tolerability was similar between 20 and 25 mg/m² BID doses based on DLT rates: 2/12 at 20 mg/m², 1/6 at 25 mg/m², 2/6 at 30 mg/m².
- (2) In SPRINT Phase II trial, a favorable efficacy/safety profile for selumetinib 25 mg/m² BID was demonstrated. Exposure-response assessment demonstrated a positive trend for AUC₀₋₂₄-efficacy (ORR) association and no clear ER relationship for safety (i.e., all grades

TEAEs, Diarrhea, Nausea, vomiting) in pediatric patients. The exposure-response assessment should be interpreted with caution because of the limitation of the study design (e.g., a single dose level pivotal trial with a small number of subjects and a high dose interruption rate).

- (3) Study in adult patients demonstrated a direct relationship between inhibition of ERK phosphorylation (substrate of MEK) and selumetinib exposure, suggesting that higher exposure contributes to greater target engagement.

6.2.2.2. Therapeutic Individualization

Data:

BSA was identified as a covariate impacting selumetinib CL and volume of distribution. BSA had more than 20% impact on CL and hence AUC (at the extremes of the observed BSA distribution). This supports BSA-based dosing in pediatrics. The posology of BSA based dosing is shown in Table 15.

The age range in the population PK analysis was wide and included individuals from the age 3 to 79 years old. The population PK analysis indicated that age has small but not a clinically relevant impact on selumetinib exposure. Age and BSA are correlated in pediatric patients and within the age range of 3 to 18 years, due to BSA based dosing, the difference in selumetinib exposure is small and unlikely to be of clinical relevance.

Table 15 Dosing Scheme of Selumetinib 25 mg/m² Twice Daily

Body surface area	Dose in mg (twice daily)	Dose level (mg/m ²)
0.55-0.69 m ²	(b) (4)	(b) (4)
0.70-0.89 m ²	20	22.5-28.6
0.90-1.09 m ²	25	22.9-27.8
1.100-1.29 m ²	30	23.3-27.3
1.30-1.49 m ²	35	23.5-26.9
1.50-1.69 m ²	40	23.7-26.7
1.70-1.89 m ²	45	23.8-26.5
≥1.90 m ²	50	<26.3

The Applicant's Position:

Therapeutic individualization based on BSA is proposed for the pediatric patients. Other demographic factors (age, gender), mild, moderate, severe renal impairment or end stage renal disease (ESRD) patients or mild hepatic impairment (based on Child-Pugh classification) have no impact on selumetinib PK. Dose adjustments are recommended for moderate hepatic impairment patients and selumetinib is not recommended in patients with severe hepatic impairment.

Impact of DDI on selumetinib PK is discussed in Section 6.3.2.

The FDA's Assessment:

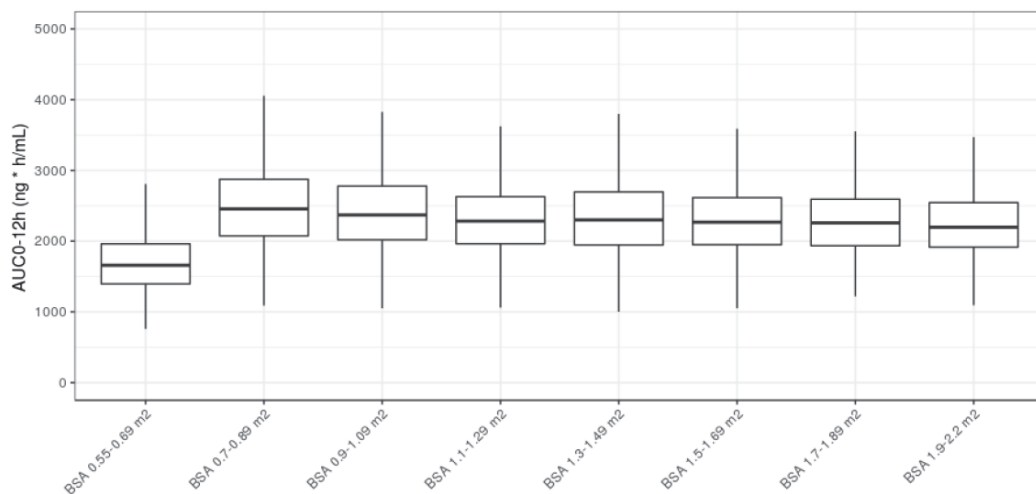
The FDA agrees with the Applicant's assessment regarding the proposed dosing regimen for patients with BSA ≥ 0.70 m² and that for age, gender, renal impairment, and mild to severe hepatic impairment. However, the FDA disagrees with the Applicant's assessment regarding the proposed dosing recommendation for patients with BSA 0.55-0.69 m².

1. Dosing guidance for patients with BSA 0.55-0.69 m²

The detailed dosing schema by BSA is based on the availability of the capsule strengths, 10 mg and 25 mg. In the Applicant proposed dosing schema of selumetinib 25 mg/m² BID (Table 2), the proposed dose for BSA 0.55-0.69 m² is (b) (4)

The mean simulated AUC_{0-12h} with the proposed (b) (4) as compared to those of the other BSA subgroups.

Figure 4 Applicant’s Simulated steady state AUC_{0-12h} across BSA bands based on Applicant’s proposed dosing schema of selumetinib 25 mg/m² BID. Source: Population PK report.



Based on the findings above, the FDA recommends a **daily dose of 30 mg for BSA 0.55-0.69 m², i.e., 20 mg morning dose and 10 mg evening dose**. This recommended dosing regimen is supported by the following rationale:

- (1) The 20 mg/10 mg dose could achieve a daily dose of 30 mg with a corresponding daily dose level of 43.5-54.6 mg/m², which is similar to that of other BSA groups.
- (2) Selumetinib exhibits dose proportionality at the dose range tested. The 20 mg/10 mg dose is expected to achieve similar AUC as compared to that of other BSA groups.
- (3) In the SPRINT Phase I study, 2 patients with BSA 0.67 m² received selumetinib 20 mg BID with acceptable tolerability. The safety of recommended morning dose of 20 mg is therefore supported.

The final recommended dosing schema BSA is as follows:

Table 16 FDA Recommended Dosing Schema of Selumetinib 25 mg/m² Twice Daily

Body surface area	Dose in mg (twice daily)	Daily Dose level (mg/m ²)
0.55-0.69 m ²	20 morning, 10 evening	43.5-54.6
0.70-0.89 m ²	20	45.0-57.1
0.90-1.09 m ²	25	45.9-55.6

Body surface area	Dose in mg (twice daily)	Daily Dose level (mg/m ²)
1.10-1.29 m ²	30	46.5-54.5
1.30-1.49 m ²	35	47.0-53.8
1.50-1.69 m ²	40	47.3-53.3
1.70-1.89 m ²	45	47.6-52.9
≥1.90 m ²	50	<52.6

2. Dose adjustment for patients with hepatic impairment

Based on the dedicated hepatic impairment study, the FDA agrees with the Applicant for a dose reduction to 20 mg/m² BID for patients with moderate hepatic impairment, and the recommended dosage cannot be established for patients with severe hepatic impairment. See Section 6.3.2 below for details.

6.2.2.3. Outstanding Issues

A comprehensive clinical pharmacology package has been conducted which has characterized the PK of selumetinib and provided appropriate dosing guidance for intrinsic/extrinsic factors, special populations and DDI.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA assessed that there is an outstanding issue of taking selumetinib on an empty stomach (fasted 2 hours before and 1 hour after each dose) due to the following reasons:

- (1) It poses difficulty for pediatric patients to take selumetinib twice daily on an empty stomach (total of 6-hour fasting time window) and may lead to compliance issues;
- (2) The food effect studies showed a greater magnitude of exposure change when selumetinib was administered with a low-fat meal as compared to a high-fat meal, which is unusual;
- (3) The incidence of gastrointestinal toxicities and dose interruptions due to gastrointestinal toxicities were high in pediatric patients;
- (4) The safety profile with regards gastrointestinal toxicities is not similar in adult patients and cannot be extrapolated to pediatric patients.

The Applicant is issued a PMR to conduct a trial to evaluate whether administration of selumetinib (as the to-be-marketed capsule formulation) with food may alleviate gastrointestinal toxicities in adolescent patients and also to confirm an appropriate dosing recommendation of selumetinib with a low-fat meal.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

The PK of selumetinib are comparable between healthy adult subjects, adult patients with advanced solid malignancies and pediatric patients with NF1 and inoperable PN aged 3 to 18 years old at the time of enrollment at the investigated dose range. The observations and conclusions from the clinical pharmacology studies performed in healthy adult subjects and adult patients are considered of direct relevance for pediatric patients. An overview of the ADME properties, clinical PK, and DDI potential of selumetinib is provided below.

Absorption: Selumetinib is a Biopharmaceutics Classification System Class IV (low solubility, low permeability) compound; however, extensive in vitro and in vivo assessments have been carried out and confirms that exposure from selumetinib capsules are not dissolution or permeability limited. Across healthy subjects and adult patients with cancer, absorption was rapid with C_{max} achieved at a median t_{max} of 1 to 1.5 hours after dosing following single oral doses of 25 to 75 mg dose of selumetinib. In pediatric patients after a single dose (SPRINT study), median t_{max} following oral dosing was 1 hour across the dose range (20 to 30 mg/m²) demonstrating similarity in the rate of absorption in pediatric, adult patients, and healthy subjects.

Absolute oral bioavailability of a single dose of selumetinib in healthy adult subjects was 62% (90% confidence interval [CI]: 60.1%, 64.1%).

Distribution: The geometric mean volume of distribution (V_{ss}) determined following selumetinib intravenous administration (Study 80) was 59.8 L (range 41.7 to 87.5 L). Apparent volume of distribution (V_{ss}/F) across the dose range studied in adult patients (25 to 100 mg) was similar to that observed in healthy adult subjects (89 to 126 L and 116 to 170 L, respectively), indicating selumetinib is moderately distributed into tissues in adults. In pediatric patients, similar to that observed in adult patients and healthy adult subjects, selumetinib appeared to be moderately distributed with geometric mean apparent volume of distribution (V_z/F) values of 78 to 171 L in the dose range of 20 to 30 mg/m².

Selumetinib was shown to be highly bound to human plasma proteins with a mean percentage binding of 98.4% in plasma from male human subjects.

Metabolism: The major metabolic pathways for selumetinib involve N-demethylation, glucuronidation and oxidation. In healthy adult subjects, selumetinib was the major circulating drug-related component and accounted for ~40% of the plasma radioactivity. In addition, other circulating metabolites in plasma were identified as a glucuronide of the imadazoindazole

metabolite (22%), a selumetinib glucuronide (7%), and N-desmethyl carboxylic acid (3.6%). The amide metabolite (AZ12791138) was quantified in human plasma to be less than 2% and is 50-fold less potent than parent and is therefore unlikely to significantly contribute to biological activity. The N-desmethyl metabolite of selumetinib (AZ12442942) is approximately 3- to 5-fold more potent in vitro than selumetinib and was quantified as ~3% of dose in human plasma (AUC ratio metabolite to parent is ~7% across clinical studies).

Excretion: The recovery of radioactivity in excreta in healthy adult subjects was collected for a total of 9 days. Over this period the total radioactivity recovered was 93% with approximately 59% excreted in feces (~19% as unchanged selumetinib) and approximately 33% recovered in urine (<1% as unchanged selumetinib).

The major component present in human urine was the glucuronide of imidazoindazole metabolite (M2) and accounted for ~10% of the radiochemical dose. Other metabolites present at >3% of the dose in the urine include the 2 selumetinib glucuronides M7 and M4 at 6.0% and 3.8%, respectively, and the N-desmethyl glucuronide (M3) at 3.4%. Unchanged selumetinib was a minor component of urine, accounting for ≤1% of the dose in all subjects.

The major component in feces was unchanged selumetinib and accounted for a mean of ~19% of the dose in the feces. Seven metabolites accounted for between 1% and 10% of the dose in feces: the predominant metabolites being the primary amide metabolite (M14 – 8.7%), the N-desmethyl amide (M12 – 6.5%) and the N-desmethyl metabolite (M8 – 6.1%). Remaining metabolites were <3% of the dose.

Clinical Pharmacokinetics: Selumetinib was rapidly absorbed after single and repeated oral BID dosing with a median t_{max} of 1 hour across the 20 to 30 mg/m² groups in pediatric patients. C_{max} and AUC increased in an approximately dose proportional manner in pediatric patients, at 20 to 30 mg/m², and in adult patients between 25 to 100 mg doses. Selumetinib had an apparent oral CL of 8.8 to 15.0 L/hour, mean apparent volume of distribution of 78 to 171 L, and the terminal half-life ranged between 6.2 to 9.4 hours in pediatric patients across the 20 to 30 mg/m² dose range. Minimal accumulation was observed on chronic BID dosing at steady state (accumulation ratio ~1.1). The observed within-subject variability (coefficient of variation [CV%]) for selumetinib AUC and C_{max} was 17% and 34%, respectively. The observed intersubject variability (CV%) for selumetinib AUC and C_{max} was 24% and 26%, respectively.

Pharmacological activity is primarily due to selumetinib. Two metabolites of selumetinib were identified to have pharmacological activity of which N-desmethyl metabolite is ~3- to 5-fold more potent than selumetinib and may contribute to safety and efficacy while the amide metabolite is ~50-fold less potent in vitro and is unlikely to contribute to safety and efficacy. The apparent elimination half-life of N-desmethyl metabolite is similar to that of parent and is

unlikely to accumulate. Based on 5% to 7% of the circulating levels, the N-desmethyl metabolite may contribute 21% to 35% of the activity of selumetinib.

Food effect: In adult patients and healthy adult subjects, consumption of a high fat meal reduces the rate of absorption (~50% decrease in C_{max} ; t_{max} delayed by 2 hours) and the extent of absorption (AUC decreases by 16% to 19%). In another study, consumption of a low-fat meal reduces the rate of absorption (65% decrease in C_{max} ; t_{max} delayed by 2.5 hours) and the extent of absorption (AUC decreases by 38%) in adult healthy subjects. In the SPRINT study, pediatric patients were administered selumetinib in the fasted state (fasting for 2 hours before and 1 hour after dosing).

Gastric acid modifying agents: Selumetinib capsule 25 mg dissolution is pH independent in which similar rates and extent of release is observed across the physiological pH range. Therefore, it is expected that drugs which modify the gastric pH (H₂-receptor antagonists and proton pump inhibitors [PPIs]) present a low risk of impacting dissolution of selumetinib capsules and consequently affecting in vivo exposure. Hence, selumetinib can be co-administered with gastric pH modifying agents without any dose modifications.

Renal impairment: Minor changes in selumetinib PK (28% and 16% reduction in AUC and C_{max} in subjects with ESRD, respectively) were observed compared to subjects with normal renal function. Selumetinib can be dosed to patients with mild, moderate, severe renal impairment or ESRD patients without dose adjustment. Dialysis has limited effect on systemic selumetinib so is unlikely to be beneficial to treat selumetinib overdose.

Hepatic impairment: Selumetinib exposure was slightly lower (14%) in the mild hepatic impairment group compared to the normal group. For subjects with either moderate or severe hepatic impairment group, total exposure (AUC) was higher compared to the normal group, by 59% and 57%, respectively. The increases in unbound AUC were higher, 41% for moderate impairment and 317% for severe impairment. In pediatric patients, no dose adjustment is required in mild hepatically impaired subjects. For patients with moderate hepatic impairment, a starting dose of 20 mg/m² is recommended. Selumetinib is not recommended for use in patients with severe hepatic impairment.

Ethnicity: Dose normalized AUC and C_{max} in healthy adult subjects of Asian ethnicity were slightly higher compared to Western subjects. However, these apparent differences were lower when AUC and C_{max} were corrected for body weight. Therefore, it is anticipated that the observed PK ethnic differences of selumetinib are likely not to be of clinical relevance, particularly as pediatric patients will follow a BSA adjusted dosing regimen of selumetinib.

Victim DDI: Selumetinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) but clinically relevant interactions are unlikely. Selumetinib is metabolized

primarily by CYP3A4 and to a minor extent by several other CYPs and UGTs including CYP2C9, CYP2C19, CYP1A2, CYP2E1, UGT1A1, and UGT1A3. In clinical studies, selumetinib exposure increased by ~50% when co-administered with the strong CYP3A4 inhibitor itraconazole or the strong CYP2C19 and moderate CYP3A4 inhibitor fluconazole. It is recommended to avoid co-administration of selumetinib and strong CYP3A4/CYP2C19 inhibitors. However, if coadministration is necessary and unavoidable, caution and monitoring may be required when co-administering selumetinib with strong CYP3A4 or CYP2C19 inhibitors. The exposure to selumetinib in healthy adult subjects was reduced by 51% when co-administered with the strong CYP3A4 inducer, rifampicin. Administration of selumetinib with strong CYP3A4 inducers should be avoided if possible.

Based on physiologically-based PK (PBPK) analysis, moderate CYP3A4 inhibitors can increase selumetinib exposure by 30% to 40% and hence, cautious use and monitoring is recommended. Moderate CYP3A4 inducer can decrease selumetinib exposure by 40% and should be avoided, if possible. Weak CYP3A4 inhibitors and inducers are unlikely to impact selumetinib exposure.

Perpetrator DDI: Based on in vitro data, selumetinib has low potential to cause clinically significant drug interactions via inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP2E1 or induction of CYP1A2, 2B6, and 3A4 enzymes or transporters (BCRP, P-gp, OATP1B1, OATP1B3, OCT2, OAT1, MATE1, and MATE2K). A clinically relevant effect on the PK of concomitantly administered substrates of OAT3 cannot be excluded.

QTc: Based on a clinical study, selumetinib does not prolong the QTc interval in healthy adult subjects and does not have any adverse effect on cardiac repolarization.

The Applicant's Position:

The current clinical pharmacology package provides characterization of the key PK properties of selumetinib and when combined with in vitro drug metabolism and PK profiling data provides sufficient data in support of the selected dose and adequate labelling for special populations and DDI. From a clinical PK perspective, these data support a BID 25 mg/m² dose for these pediatric patients with NF1 and inoperable PN.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of the general pharmacology and pharmacokinetics of selumetinib; however, the FDA has different dosing recommendations for DDI. See Section 6.3.2 below for details. The bioanalytical methods are summarized in the OCP Appendices.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Yes. The results of the exposure-response analysis for both efficacy and safety did not indicate a clear relationship between selumetinib exposure and response within the exposure range investigated in the SPRINT study using the BSA based dosing regimen. At the recommended daily dose of 25 mg/m² BID, a positive benefit/risk profile that maximizes clinical activity in patients, while simultaneously minimizing the incidence and severity of adverse reactions as well as dose modifications was noted. The starting dose of 25 mg/m² BID also allows for a potential for dose reduction to 20 mg/m² in case of tolerability issues which has also shown clinical activity. Importantly, the 25 mg/m² ensures that patients will receive a clinically active dose regardless of inter-patient variability and allows prescribers to reduce the dose should this be necessary. Appropriate dose adjustment guidance is provided in the proposed labelling.

The Applicant's Position:

The proposed dosing regimen of 25 mg/m² BID based on BSA is suitable for pediatric patients with NF1 who have symptomatic, inoperable PN.

The FDA's Assessment:

The FDA generally agrees with the Applicant's exposure-response analyses to provide supportive evidence of effectiveness.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Yes. BSA was identified as a covariate impacting selumetinib clearance and volume of distribution. The proposed BSA based dosing in pediatric patients is appropriate as this is shown to be effective and generally well tolerated with no difference between gender. Simulation of 1000 patients at each band with their corresponding median and 75% prediction interval at the 25 mg/m² dose indicates that the BSA based dosing is predicted to provide similar exposure across bands and ensures that all pediatric patients will be dosed in the range of the recommended dose of 25 mg/m².

Adverse events (AEs) were transient and was effectively managed with concomitant medications or dose modifications as needed. The number of patients with dose modifications (interruptions or reductions) was low (<25%) indicating that the dose of 25 mg/m² BID is generally well tolerated and appropriate for this patient population.

The Applicant's Position:

The BSA based dosing regimen of 25 mg/m² BID is appropriate for pediatric patients with NF1 and inoperable PN.

The FDA's Assessment:

The FDA generally agrees with the Applicant's proposed dosing regimen of selumetinib 25 mg/m² BID for the proposed indication in pediatric patients. The FDA recommends dosing regimen of 20 mg morning dose and 10 mg evening dose for patients with BSA 0.55-0.69 m². See Section 6.2.2.2.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Data:

Hepatic impairment: Selumetinib exposure was slightly lower (14%) in the mild hepatic impairment group compared to the normal group. For subjects with either moderate or severe hepatic impairment group, total exposure (AUC) was higher compared to the normal group, by 59% and 57%, respectively. The increases in unbound AUC were higher, 41% for moderate impairment and 317% for severe impairment. In pediatric patients, no dose adjustment is required in mild hepatically impaired subjects. For patients with moderate hepatic impairment, starting dose of 20 mg/m² is recommended. Selumetinib is not recommended for use in patients with severe hepatic impairment.

Renal impairment: Minor changes in selumetinib PK (28% and 16% reduction in AUC and C_{max} in subjects with ESRD, respectively) were observed compared to subjects with normal renal function. Selumetinib can be dosed to patients with mild, moderate, severe renal impairment or ESRD patients without dose adjustment. Dialysis has limited effect on systemic selumetinib so is unlikely to be beneficial to treat selumetinib overdose.

Ethnicity: Dose normalized AUC and C_{max} in healthy adult subjects of Asian ethnicity were slightly higher compared to Western subjects. However, these apparent differences were lower when AUC and C_{max} were corrected for body weight. Therefore, it is anticipated that the observed PK ethnic differences of selumetinib are likely not to be of clinical relevance, particularly as pediatric patients will follow a BSA adjusted dosing regimen of selumetinib.

The Applicant's Position:

Based on the assessment of intrinsic factors, dose adjustment is required for moderate hepatic impairment (Child Pugh B) and is not recommended for patients with severe hepatic impairment (Child Pugh C). For renal impairment and other demographics (age, gender, and ethnicity), no dose adjustment is required.

The FDA's Assessment:

Given that the N-desmethyl metabolite of selumetinib has 3-5 fold greater potency in vitro than selumetinib, FDA considered six molar-normalized exposure matrices in addition to selumetinib AUC and C_{max} : total moiety AUC, total moiety C_{max} , potency-adjusted total moiety AUC, potency-adjusted total moiety C_{max} , potency-adjusted unbound moiety AUC (adjusted free total moiety), and potency-adjusted unbound moiety C_{max} (adjusted free total moiety). Results were similar across all exposure matrices; therefore, dose adjustments for intrinsic patient factors are based on selumetinib exposures.

The FDA agrees with the Applicant that selumetinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C). Based on results from the hepatic impairment study that showed a 3.17-fold (90% CI: 2.24, 4.50) increase in unbound AUC in subjects with severe hepatic impairment as compared to subjects with normal hepatic function, a dose reduction to 10 mg/m² BID based on exposure matching would be recommended. However, considering the limited available dose strengths of selumetinib 10 and 25 mg capsules, a recommended dosing nomogram cannot be established. Furthermore, the potential for pediatric patients with NF1 to have severe hepatic impairment is low. Therefore, the FDA agrees that no dose recommendation could be made for patients with severe hepatic impairment at this stage. Should any alternative dosage form be available in the future, the FDA may re-evaluate the feasibility of dosing recommendations for patients with severe hepatic impairment.

The FDA agrees with the Applicant's dosing recommendation to reduce the dose of selumetinib to 20 mg/m² BID in patients with moderate hepatic impairment (Child-Pugh B) based on results from the hepatic impairment study that showed a 41% increase in unbound AUC in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function. See DDI section below (Table 17) for the dosing regimen of 20 mg/m² BID for different BSA subgroups.

The FDA agrees with the Applicant that no dose adjustment is needed for mild hepatic impairment, renal impairment, sex, and race/ethnicity based on the data provided.

6.3.2.4 Are there clinically relevant food-drug or DDIs, and what is the appropriate management strategy?

Data:

The clinically relevant food-drug and DDIs with concomitant medications are described in further detail below with their respective recommendation for management.

Food effect: In adult patients and healthy adult subjects, consumption of a high fat meal reduces the rate of absorption (~50% decrease in C_{max} ; t_{max} delayed by 2 hours) and the extent of absorption (AUC decreases by 16% to 19%). In another study, consumption of a low-fat meal

reduces the rate of absorption (65% decrease in C_{max} ; t_{max} delayed by 2.5 hours) and the extent of absorption (AUC decreases by 38%) in adult healthy subjects. In the SPRINT study, pediatric patients were administered selumetinib in the fasted state (fasting for 2 hours before and 1 hour after dosing).

Gastric pH: Selumetinib capsule 25 mg dissolution is pH independent in which similar rates and extent of release is observed across the physiological pH range. Therefore, it is expected that drugs which modify the gastric pH (H₂-receptor antagonists and PPIs) present a low risk of impacting dissolution of selumetinib capsules and consequently affecting in vivo exposure. Hence, selumetinib can be co-administered with gastric pH modifying agents without any dose modifications.

Victim DDI: Selumetinib is a substrate of P-gp and BCRP but clinically relevant interactions are unlikely. Selumetinib is metabolized primarily by CYP3A4 and to a minor extent by several other CYPs and UGTs including CYP2C9, CYP2C19, CYP1A2, CYP2E1, UGT1A1, and UGT1A3. In clinical studies, selumetinib exposure increased by ~50% when co-administered with the strong CYP3A4 inhibitor itraconazole or the strong CYP2C19 and moderate CYP3A4 inhibitor fluconazole. It is recommended to avoid co-administration of selumetinib and strong CYP3A4/CYP2C19 inhibitors. However, if coadministration is necessary and unavoidable, caution and monitoring may be required when co-administering selumetinib with strong CYP3A4 or CYP2C19 inhibitors. The exposure to selumetinib in healthy adult subjects was reduced by 51% when co-administered with the strong CYP3A4 inducer, rifampicin. Administration of selumetinib with strong CYP3A4 inducers should be avoided if possible.

Based on PBPK analysis, moderate CYP3A4 inhibitors can increase selumetinib exposure by 30% to 40% and hence, cautious use and monitoring is recommended. Moderate CYP3A4 inducer can decrease selumetinib exposure by 40% and should be avoided, if possible. Weak CYP3A4 inhibitors and inducers is unlikely to impact selumetinib exposure.

Perpetrator DDI: Based on in vitro data, selumetinib has low potential to cause clinically significant drug interactions via inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP2E1 or induction of CYP1A2, 2B6 and 3A4 enzymes or transporters (BCRP, P-gp, OATP1B1, OATP1B3, OCT2, OAT1, MATE1, and MATE2K). A clinically relevant effect on the PK of concomitantly administered substrates of OAT3 cannot be excluded.

The Applicant's Position:

Based on in vitro and clinical studies, appropriate management strategy for food, gastric pH, and DDI is proposed.

The FDA's Assessment:

Given that the N-desmethyl metabolite of selumetinib has 3-5 fold greater potency in vitro than selumetinib, FDA considered six molar-normalized exposure matrices in addition to selumetinib AUC and C_{max} : total moiety AUC, total moiety C_{max} , potency-adjusted total moiety AUC, potency-adjusted total moiety C_{max} , potency-adjusted unbound moiety AUC (adjusted free total moiety), and potency-adjusted unbound moiety C_{max} (adjusted free total moiety). Results were similar across all exposure matrices; therefore, dose adjustments for extrinsic patient factors are based on selumetinib exposures.

The FDA has concerns with the Applicant's recommendation with regards to food. The FDA disagrees with the Applicant's dosing recommendations with regards to DDI.

(1) Dosing recommendation for selumetinib with regards to food

In Phase 1 and Phase 2 of the SPRINT study, selumetinib was taken in the fasted state. The FDA agrees with the Applicant's proposal to take selumetinib on an empty stomach based on currently available data that showed a 38% decrease in AUC (90% CI: 30%, 45%) when taking selumetinib with a low-fat meal as compared to fasted state, and exposure-response analyses that suggests decreased exposure may lead to decreased efficacy and target engagement. Although a high-fat meal showed minimal effect on selumetinib AUC, it is not feasible to recommend taking selumetinib with a high-fat meal. Given limitations of currently available data, the FDA recommends collecting additional PK and safety data via a PMR study to determine an appropriate dosing regimen of selumetinib with food that may alleviate gastrointestinal toxicities in pediatric patients. See Outstanding Issues.

(2) Dosing recommendation with regards to DDI

In the PBPK modelling, it was predicted that selumetinib AUC increased by ~40% when co-administered with a moderate CYP3A4 inhibitor, erythromycin, and reduced by ~40% when co-administered with a moderate CYP3A4 inducer, efavirenz. See Section 19.4.

Strong or Moderate CYP3A4 Inhibitors or Fluconazole: The FDA disagrees with the Applicant's recommendation to avoid coadministration of strong CYP3A4/CYP2C19 inhibitors (b) (4) [REDACTED]. Based on results from the DDI study with itraconazole (strong CYP3A4 inhibitor) that showed a 49% (90% CI: 40, 59) increase in selumetinib AUC, the FDA recommends dose reduction by approximately 30%:

- If patient is currently taking 25 mg/m² BID, dose reduce to 20 mg/m² BID
- If patient is currently taking 20 mg/m² BID, dose reduce to 15 mg/m² BID

Table 17 Dosing Schema for Selumetinib 20 mg/m² Twice Daily and 15 mg/mg² Twice Daily

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

Based on results from the DDI study with fluconazole (strong CYP2C19 inhibitor/moderate CYP3A4 inhibitor) that showed a 53% (90% CI: 44, 63) increase in selumetinib AUC, FDA recommends similar dose reductions as those for coadministration with strong CYP3A4 inhibitors. Based on PBPK modeling that showed concomitant use of erythromycin (moderate CYP3A4 inhibitor) is predicted to increase selumetinib AUC by ~40%, FDA recommends similar dose reductions as those for coadministration with strong CYP3A4 inhibitors.

Strong and moderate CYP3A4 inducers: Given both selumetinib and the active metabolite N-desmethyl selumetinib are metabolized by CYP3A4 and both strong and moderate CYP3A4 inducers were observed and predicted to reduce selumetinib AUC by ~40%-50%, the FDA agrees with the Applicant that strong and moderate CYP3A4 inducers should be avoided when administering selumetinib to avoid potential loss of efficacy due to decreased drug exposure. An increase in selumetinib dose by exposure matching is not recommended due to the unknown effect of selumetinib solubility on its PK at higher doses and limited information on the safety of the N-desmethyl metabolite.

Acid reducing agents: The FDA agrees that selumetinib does not exhibit pH-dependent solubility based on the in vitro dissolution testing on selumetinib hydra-sulfate capsule at pH 1.2, 4.5, 6.5. Therefore, a DDI study with an acid reducing agent does not need to be conducted.

Transporters: The FDA agrees that selumetinib is a substrate of P-gp and BCRP, but clinically relevant interactions are unlikely.

Effect of Selumetinib on Other Drugs: FDA agrees that selumetinib and its active N-desmethyl metabolite do not inhibit or induce CYP enzymes, and do not inhibit transporters to a clinically relevant extent based on in vitro studies.

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Koselugo (selumetinib)

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Table 18 Listing of Clinical Trials Relevant to this NDA

Trial Identity (NCT number)	Trial Design	Regimen and Schedule	Primary Objective	Treatment Duration/Follow-up	Study Population	Number of Patients, Centres and Countries
Studies to Support Safety and Efficacy						
Study 8799; NCI 11-C-0161; D1532C00057 ; SPRINT Phase II, Stratum 1 (01362803)	Open-label, single-arm, multi-centre study of selumetinib in children with NF1 and inoperable PN, with PN related morbidity at enrolment.	Selumetinib hyd-sulfate capsule 25 mg/m ² BID on a continuous dosing schedule (1 cycle=28 days)	Evaluate confirmed partial and complete response rate of selumetinib using volumetric MRI analysis in children and young adults with NF1 and inoperable PN with PN-related morbidity at time of enrolment.	Treatment duration was determined to ensure that patients had the opportunity to derive benefit but was limited based on whether they had documented disease progression within approx. 1.5 years prior to study entry: With: no limit to duration of treatment as long as patient met requirements for further treatment. Without: limited to 2 years if no imaging response.	Pediatric patients with NF1 and inoperable PN with PN-related morbidity at enrolment.	50 patients/ 4 sites/ 1 country (USA)

Table 18 Listing of Clinical Trials Relevant to this NDA

Trial Identity (NCT number)	Trial Design	Regimen and Schedule	Primary Objective	Treatment Duration/Follow-up	Study Population	Number of Patients, Centres and Countries
Study 8799; NCI 11-C-0161; D1532C00057 ; SPRINT Phase I (01362803)	Open-label, single-arm, dose escalation, multi-centre study of selumetinib in children with NF1 and inoperable PN.	Selumetinib hyd-sulfate capsule 20 mg/m ² BID on a continuous dosing schedule (1 cycle=28 days) escalated to selumetinib 30 mg/m ² BID	To determine the MTD, extended tolerability, and recommended Phase II dose of selumetinib administered orally every 12 hours on a continuous daily schedule for cycles of 28 days with no rest period between cycles in children and adolescents with NF1 and inoperable PN; study the plasma PK of selumetinib at baseline and steady state.	Treatment duration was determined to ensure that patients had the opportunity to derive benefit but was limited based on whether they had documented disease progression within approx. 1.5 years prior to study entry: With: no limit to duration of treatment as long as patient met requirements for further treatment. Without: limited to 2 years if no imaging response.	Pediatric patients with NF1 and inoperable PN.	24 patients/ 4 sites/ 1 country (USA)
Studies to Support Safety						
D1532C00003 (00338130)	Phase II Randomized, open-label study to assess efficacy of selumetinib versus temozolomide.	Selumetinib free-base suspension Selumetinib 100 mg BID vs Temozolomide 200 mg/m ² daily for 5 days every 28 days	To compare the efficacy of selumetinib versus temozolomide.	12 weeks, although patients could continue treatment until disease progression, provided they were deriving clinical benefit (in the opinion of the investigator), in the absence of unacceptable toxicity.	Adult patients with unresectable AJCC Stage 3 or 4 malignant melanoma	194 patients/ 33 sites/ 10 countries

Table 18 Listing of Clinical Trials Relevant to this NDA

Trial Identity (NCT number)	Trial Design	Regimen and Schedule	Primary Objective	Treatment Duration/Follow-up	Study Population	Number of Patients, Centres and Countries
D1532C00005 (00463814)	Phase I, open label study to assess safety, tolerability and PK of the capsule formulation; and relative bioavailability of single dose free-base and capsule formulations.	Selumetinib hyd-sulfate capsule selumetinib free-base suspension Part A: 25, 50, 75, 100 mg BID hyd-sulfate Part B: single dose 75 mg hyd-sulfate vs 100 mg free-base. Patients received continuous BID dosing of the hyd-sulfate capsule from Part B Day 9 onwards.	Assess the safety and tolerability of the capsule formulation of selumetinib in patients with advanced solid malignancies.	Until disease progression as long as they were continuing to derive benefit from treatment.	Adult patients with advanced solid malignancies.	60 patients/ 4 sites/ 3 countries

Table 18 Listing of Clinical Trials Relevant to this NDA

Trial Identity (NCT number)	Trial Design	Regimen and Schedule	Primary Objective	Treatment Duration/Follow-up	Study Population	Number of Patients, Centres and Countries
D1532C00008 (00372944)	Phase II Randomized, open-label, study to assess efficacy and safety of selumetinib vs capecitabine.	Selumetinib free-base suspension Selumetinib 100 mg BID vs capecitabine 1250 mg/m ² BID orally for 2 weeks, followed by a 1-week rest period.	To assess the efficacy of selumetinib versus capecitabine in the treatment of advanced or metastatic pancreatic cancer by assessment of time to death.	Until objective and/or clinical progression, provided deriving clinical benefit, in absence of unacceptable toxicity and provided patient was willing to continue.	Adult patients with advanced or metastatic pancreatic cancer, failed first-line gemcitabine therapy.	70 patients/ 17 sites/ 5 countries
D1532C00011 (00514761)	Phase II Randomized, open-label, study to assess efficacy and safety of selumetinib vs capecitabine.	Selumetinib free-base suspension Selumetinib 100 mg BID vs capecitabine 1250 mg/m ² BID orally for 2 weeks, followed by a 1-week rest period.	To assess the efficacy of selumetinib versus capecitabine in the treatment of metastatic colorectal cancer by assessment of disease progression.	Until objective and/or clinical progression, provided deriving clinical benefit, in absence of unacceptable toxicity and provided patient was willing to continue.	Adult patients with colorectal cancer, failed at least 1 prior chemotherapy regimen.	69 patients/ 3 sites/ 1 country

Table 18 Listing of Clinical Trials Relevant to this NDA

Trial Identity (NCT number)	Trial Design	Regimen and Schedule	Primary Objective	Treatment Duration/Follow-up	Study Population	Number of Patients, Centres and Countries
D1532C00012 (00372788)	Phase II Randomized, open-label, study to assess efficacy and safety of selumetinib vs pemetrexed.	Selumetinib free-base suspension Selumetinib 100 mg BID vs pemetrexed 500 mg/m ²	To assess the efficacy of selumetinib versus pemetrexed in the second or third-line treatment of advanced NSCLC by assessment of disease progression.	Until objective and/or clinical progression, provided deriving clinical benefit, in absence of unacceptable toxicity and provided patient was willing to continue.	Adult patients with NSCLC, failed 1 or 2 prior chemotherapy regimens.	84 patients/ 8 sites/ 3 countries
D1532C00020 (00710515)	Phase I, Open label, crossover study to assess the effect of dosing in the presence and absence of food on PK, safety and tolerability.	Selumetinib hyd-sulfate capsule 75 mg BID	To assess whether food influences the rate and extent of selumetinib absorption.	2 single doses initially; in extension until disease progression and for as long as they continued to derive benefit from treatment.	Adult patients with advanced solid malignancies.	31 patients/ 6 sites/ 2 countries

Table 18 Listing of Clinical Trials Relevant to this NDA

Trial Identity (NCT number)	Trial Design	Regimen and Schedule	Primary Objective	Treatment Duration/Follow-up	Study Population	Number of Patients, Centres and Countries
D1344C00001 (01974752)	Phase III Randomized, double-blind study to assess the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine.	Selumetinib hyd-sulfate capsule Selumetinib 75 mg BID plus dacarbazine 1000 mg/m ² q21d	To assess the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine in terms of PFS.	Until objective disease progression, intolerable toxicity or the occurrence of another discontinuation criterion.	Adult patients with metastatic uveal melanoma receiving first-line treatment	129 patients/ 31 sites/ 11 countries

AJCC American Joint Committee on Cancer; BID Twice daily; BLA Biologics license application; CSR Clinical study report; hyd-sulfate Hydrogen sulfate; MRI Magnetic resonance imaging; MTD Maximum tolerated dose; NCI National Cancer Institute; NF1 Neurofibromatosis type 1; NDA New drug application; NSCLC Non-small cell lung cancer; PFS Progression-free survival; PK Pharmacokinetics; PN Plexiform neurofibromas; q21d Every 21 days; USA United States of America.

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The Applicant's Position:

Table 18 presents the studies used to support efficacy for selumetinib in the proposed indication, in addition to studies that are included in the safety dataset.

The FDA's Assessment:

The FDA agrees with the Applicant's descriptions of the studies as outlined in Table 3. The primary efficacy results supporting the NDA are from SPRINT Phase II Stratum 1 (N=50). The primary safety results supporting the NDA are from SPRINT Phase I pooled with SPRINT Phase II Stratum 1 (N=74). Supportive safety data in the NDA comes from pooled results of seven studies of single-agent selumetinib in adult patients with various cancers. The specific studies included in this supportive safety pool are listed under "Studies to Support Safety" in Table 18.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. SPRINT Phase II Stratum 1

Trial Design

The Applicant's Description:

SPRINT Phase II Stratum 1, is an open-label, single-arm, multi-centre study of selumetinib in children with NF1 and inoperable PN, with PN-related morbidity at enrolment. Pediatric oncologists with extensive experience in performing investigational drug studies in children conducted this study. For SPRINT Phase II, patients were enrolled on 1 of 2 strata based on whether they already had PN-related morbidity (Stratum 1) or had no significant clinical morbidity but the potential for significant clinical PN-related morbidity (Stratum 2) at the time of enrolment. At the time of data cut-off (DCO) for this application, Stratum 2 is insufficiently mature and therefore not included in this submission.

Fifty patients aged ≥ 2 and ≤ 18 years with NF1 and inoperable PN and PN-related morbidity present at enrolment were to receive selumetinib 25 mg/m² BID. Patients were to have a Karnofsky performance level of $\geq 70\%$ (for patients aged >16 years) or a Lansky performance of $\geq 70\%$ (for patients aged ≤ 16 years old). Patients were enrolled irrespective of their PN progression status at baseline (progressive PN were defined as those having $\geq 20\%$ increase in PN volume within 12 to 15 months prior to enrolment). Clinically relevant PN-related morbidity at baseline was determined by the investigator at the time of study entry. Patients must have had a BSA of ≥ 0.55 m², and the ability to swallow whole capsules. For patients who either had progressive PN at baseline or if they did not have progressive PN at baseline and did respond, then they continued on treatment as long as they were deriving clinical benefit or until they met at least 1 of the off-study criteria. If the patient did not have progressive PN at baseline nor had achieved a response with 2 years, then treatment was discontinued.

Patients were to be followed up for 5 years after completing selumetinib, or for a total duration of 7 years, whichever was longer.

Trial Location

The study was sponsored by Cancer Therapy Evaluation Programme (CTEP) and conducted by the NCI POB (co-ordinating site) at 4 sites in the US.

External Control Data

NCI POB NF1 Natural History Study

The Natural History study is a prospective study in patients with NF1, which is sponsored and conducted by the NCI POB. It enrolls both pediatric and adult patients aged ≤ 35 years old with a clinical diagnosis of NF1 or a confirmed NF1 mutation, patients are not required to have PN-related morbidity at enrolment.

Patients had serial evaluations of their PN yearly until age 18 and thereafter at least every 3 years. Only 1 PN (most clinically-relevant “typical” PN) per patient was selected for analysis and only the volumetric magnetic resonance imaging (MRI) data of the same PN in each patient, which had been followed up for the longest period of time, not affected by surgery or a MEK inhibitor, was selected to be included in the Natural History analysis. If a patient received treatment with a MEK inhibitor (including selumetinib) during the Natural History study, data collected during the MEK inhibitor treatment period have been excluded from the analysis of Natural History study data.

The PN volume data from patients with at least 2 volumetric MRIs in this study whose baseline volumetric MRI assessments occurred aged ≥ 3 to ≤ 18 years (known as the age-matched population) were analysed by AstraZeneca.

Placebo Arm of Tipifarnib Study 01-C-0222

Study 01-C-0222 was sponsored by CTEP and coordinated by the NCI POB. This was a multi-centre, double-blinded, placebo-controlled, randomized, cross-over study of tipifarnib (R115777) in children and young adults (≥ 3 and ≤ 25 years) with a clinical diagnosis of NF1 and unresectable, progressive PN with the potential to cause significant morbidity (progressive $\geq 20\%$ increase in PN volume, or $\geq 13\%$ increase in 2-dimensional, or $\geq 6\%$ increase in 1-dimensional measurement over last 2 consecutive volumetric MRI scans or within approximately 1 year prior to trial evaluation). Patients were randomized to receive tipifarnib (200 mg/m² orally every 12 hours) or placebo (Phase A) and crossed over to the opposite treatment arm at the time of PN progression (Phase B). In each 28-day treatment cycle, study treatment was administered for 21 days followed by a 7-day rest period.

PN growth during the study was monitored using volumetric MRI. Volumetric MRI of up to 3 most clinically relevant target PN was performed prior to the start of Cycles 1, 4, 7 and 10 and then after every 6 cycles (1 cycle=28 days). All volumetric MRIs were sent to the NCI POB for central analysis with review of the scans being performed by the same single expert reader as in SPRINT Phase II Stratum 1. A volumetric increase of $\geq 20\%$ in at least 1 PN compared with baseline was defined as progressive disease.

The placebo arm from Phase A (first period of cross-over; N=29) of the study was used as an external control for patients from SPRINT Phase II Stratum 1 for time to progression (TTP) and

progression-free survival (PFS) endpoints. Patients in the placebo arm of Phase A ranged in age from ≥ 3 to ≤ 18 years.

All the volumetric MRIs in both the NCI POB NF1 Natural History study and in the placebo arm of the tipifarnib Study 01-C-0222 were evaluated by the same single expert reader as in SPRINT Phase II Stratum 1. PN progression was defined as a $\geq 20\%$ increase in PN volume compared with baseline.

Diagnostic Criteria:

Children with NF1 and inoperable PN, with PN-related morbidity at enrolment as determined by the NCI POB. Refer to study design section above.

Eligibility:

Key Inclusion Criteria

For inclusion in SPRINT Phase II Stratum 1, patients had to fulfil all of the following criteria (per Protocol Amendment N):

1. Age: ≥ 2 and ≤ 18 years at the time of enrolment to SPRINT Phase II. Body surface area ≥ 0.55 m² and ability to swallow whole capsules (assessed at screening using an empty capsule shell). The age criteria were chosen because early childhood and puberty are considered to be the greatest risk for disease progression, and selumetinib may provide the most benefit to this young group of patients.
2. Diagnosis: patients with NF1 and inoperable PN, defined as PN that could not be surgically completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN. The PN had to cause significant morbidity, such as (but not limited to) head and neck PN that could have compromised the airway or great vessels, paraspinal PN that could have caused myelopathy, brachial or lumbar plexus PN that could have caused nerve compression and loss of function, PN that could have resulted in major deformity (e.g., orbital PN) or were significantly disfiguring, PN of the extremity that could have caused limb hypertrophy or loss of function, and painful PN.
3. Measurable disease: patients must have had at least 1 measurable PN, defined as a PN of at least 3 cm measured in 1 dimension. Patients who had undergone surgery for resection of a PN were eligible, provided the PN had been incompletely resected and was measurable. Measurability and suitability for volumetric MRI analysis of the target PN had to be confirmed with the NCI POB prior to enrolment. The target PN was defined as the clinically most relevant PN, which had to be amenable to volumetric MRI analysis.

4. Prior therapy: patients with NF1 were only eligible if complete PN resection was not considered to be feasible without substantial risk or morbidity.
 - Patients who had received previous investigational agents or biologic therapy, such as tipifarnib, pirfenidone, Peg-Intron, sorafenib, imatinib, or other targeted therapies were eligible for enrolment. At least 4 weeks must have elapsed since receiving medical therapy directed at the PN. Patients who received prior medical therapy for their PN must have recovered from the acute toxic effects of all prior therapy to Grade ≤ 1 Common Terminology Criteria for Adverse Events (CTCAE) v4 before entering this study.
5. Performance status: patients >16 years of age must have had a Karnofsky performance level of $\geq 70\%$, and children ≤ 16 years old must have had a Lansky performance of $\geq 70\%$.
6. Cardiac function: normal ejection fraction (echocardiogram [ECHO] or cardiac MRI) $\geq 53\%$ (or the institutional normal; if a range was given then the upper value of the range was used).
7. Informed consent.

Key Exclusion Criteria

Any of the following was regarded as a criterion for exclusion from SPRINT Phase II:

1. Pregnant or breast-feeding females were excluded due to potential risks of fetal and teratogenic AEs of an investigational agent.
2. Inability to swallow capsules, since capsules cannot be crushed or broken.
3. Prior treatment with selumetinib or another specific MEK1/2 inhibitor (unless the patient met criteria for re-treatment).

Dose Selection:

Selection of the 25 mg/m² BID on a continuous dosing schedule (28 days=1 treatment cycle) with no rest period between cycles as confirmed during SPRINT Phase I.

Dose Modification and Dose Discontinuation:

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

Procedures and Schedule:

Table 19 Schedule of Activities for SPRINT Phase II

Activity	Pre-study	During Cycle 1	Prior to Subsequent Cycles ¹	End of Therapy Evaluation ²	Long Term Follow-up ³
History ⁴	X	Pre-Week 3 (±3 business days)	Prior to Cycles 2-5, then every other cycle (prior to Cycles 7, 9, 11 and 13), then every 4 cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycle 31, 37, 43, etc.)	X	Annual with targeted questionnaire
Physical exam and vital signs ⁵	X	Pre-Week 3 (±3 business days)	Prior to Cycles 2-5, then every other cycle (prior to Cycles 7, 9, 11 and 13), then every 4 cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycle 31, 37, 43, etc.)	X	Annual
Height, weight, BSA ⁶	X	-	Prior to Cycles 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to Cycles 31, 37, 43, etc.)	-	Annual
Performance status and Tanner stage ⁷	X	-	Prior to Cycles 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to Cycles 31, 37, 43, etc.)	X	Annual
ECG	X	-	As clinically indicated	-	-
Echocardiogram ⁸	X	-	Prior to Cycles 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to Cycles 31, 37, 43, etc.)	X	Annually if LVEF is abnormal at the end of therapy
CBC, differential, platelets ⁹	X	-	Prior to Cycles 2-5, then every other cycle (prior to Cycles 7, 9, 11 and 13), then every 4 cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycle 31, 37, 43, etc.)	X	Annual
Urinalysis	X	-	Prior to Cycles 5, 9 and 13, then every 4 cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycles 31, 37, 43, etc.)	X	At PI discretion
Electrolytes including Ca ²⁺ , PO ⁴ , Mg ²⁺ , BUN, creatinine, glucose, ALT, AST, bilirubin, total protein/albumin, amylase, lipase, CPK ¹⁰	X	-	Prior to Cycles 2-5, then every other cycle (prior to Cycles 7, 9, 11 and 13), then every 4 cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycle 31, 37, 43, etc.)	X	Annual and if clinically indicated
PN location forms ¹¹		-	-	-	-

Table 19 Schedule of Activities for SPRINT Phase II

Activity	Pre-study	During Cycle 1	Prior to Subsequent Cycles ¹	End of Therapy Evaluation ²	Long Term Follow-up ³
PN disease evaluation ¹²	X	-	Prior to Cycles 5, 9 and 13, then every 4 cycles (prior to Cycles 17, 21 and 25), then every 6 cycles (prior to Cycles 31, 37, 43, etc.)	X	Every 6 months, then yearly x2, then every 2 years or as clinically indicated
Photography of visible PN (in consenting patients) ¹³	X	-	Prior to Cycles 5, 9 and 13, then after every 12 cycles (prior to Cycles 25, 37, etc.)	-	-
Symptom checklist ¹⁴	X	-	Prior to Cycles 3, 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to cycles 31, 37, 43, etc.)	X	-
Ophthalmology toxicity evaluation ¹⁵	X	-	Prior to Cycles 5 and 13, then yearly or more often as clinically indicated	X	As clinically indicated
Pregnancy test ¹⁶	X	-	Prior to imaging studies: prior to Cycles 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to Cycles 31, 37, 43, etc.)	-	-
Adherence questionnaire ¹⁷	RMQ only	-	Calculated for every cycle for the first year. To be calculated when patient returns for follow-up visits.	-	-
Patient diary and capsule count ¹⁹	-	-	Prior to Cycles 3, 5, 9, 13, 17, 21 and 25, then after every 6 cycles (prior to Cycles 31, 37, 43, etc.)	-	-
Quality of life and pain evaluations ¹⁸	X	-	Prior to Cycles 3, 5, 9 and 13, then after every 12 cycles (prior to cycles 25, 37, etc.)	X	-
Functional PRO assessments ¹⁸	X	-	Prior to Cycles 3, 5, 9 and 13, then after every 12 cycles (prior to Cycles 25, 37, etc.)	X	-
Endurance evaluation ¹⁹	X	-	Prior to Cycles 5, 9 and 13, then after every 12 cycles (prior to Cycles 25, 37, etc.)	X	-
Functional evaluations: orbit PN, airway PN, motor PN, bowel-bladder PN ^{20, 21, 22}	X	-	Prior to Cycles 5, 9 and 13, then after every 12 cycles (prior to Cycles 25, 37, etc.)	X	-
Sleep study ²³	X	-	Prior to Cycles 5, 9 and 13, then after every 12 cycles (prior to Cycles 25, 37, etc.)	X	As clinically indicated

Table 19 Schedule of Activities for SPRINT Phase II

Activity	Pre-study	During Cycle 1	Prior to Subsequent Cycles ¹	End of Therapy Evaluation ²	Long Term Follow-up ³
DEXA ⁴ (NCI POB only)	X	-	Prior to Cycle 13 (±2 cycles) if baseline is abnormal	-	As clinically indicated
Pharmacokinetics ²⁴	X	X	Prior to Cycles 2 or 3 ¹	-	-
Pharmacodynamics: cytokines, bone marrow derived precursor cells ²⁵	X	-	Prior to Cycles 3, 5, 9 and 13 and if feasible, at time of progression	-	-
ERK: phospho-ERK assay ²⁶	X	X	Prior to Cycles 2 or 3	-	-

¹ Days 27-28 (±14 days) of the preceding cycle. Treatment was not held while end of cycle evaluations were ongoing.

² Performed, if possible, when the patient came off treatment (regardless of the reason), unless the test or procedure had been performed within the time period defined in CSP Section 3.6.1.

³ Long term safety follow up was carried out annually (±2 months) for either 7 years following initiation of treatment or 5 years after study drug discontinuation, whichever was the longer period.

⁴ Baseline history included prior treatment for the PN (with dates). Interval history included events and changes since the last visit.

⁵ A complete standard physical examination was performed at baseline; subsequent physical exams were targeted based on signs and symptoms of the presenting patient. Vital signs: heart rate, temperature, BP, respiratory rate and oxygen saturation by pulse oximetry at baseline, and then as clinically indicated. Isolated missing vital signs were noted but not reported as protocol deviations.

⁶ BSA was calculated during the restaging visits from an average of 3 repeated measurements of weight and height, on the same day, by using a standard formula consistently at participating sites. Any BSA calculations from <3 measurements were noted but not reported as protocol deviations.

⁷ Prior to the cycle indicated in the table. See CSP Appendix IA for performance status scales/scores. Tanner stage documentation, if feasible.

⁸ Patients who stopped selumetinib for cardiac toxicity were monitored by ECHO or cardiac MRI every 3 to 6 weeks. Upon recovery from the toxicity, patients were monitored with an ECHO or cardiac MRI every 2 to 3 cycles as directed by the cardiologist (see CSP Sections 3.3.1 and 3.6).

⁹ For patients who developed Grade 4 neutropenia, CBC was checked every 3 to 4 days until recovery to Grade 1. Isolated missing lab values were noted but not reported as protocol deviations.

¹⁰ CPK isoenzymes were drawn for CPK ≥Grade 2 (X1); this needed to be done once only. Isolated missing lab values were noted but not reported as protocol deviations.

¹¹ The PN location and morbidity form was completed by the site PI. The PN location and classification form was completed by the NCI (see CSP Appendix IIB).

¹² Volumetric MRI (see CSP Appendix IIA).

¹³ See CSP Appendix IV.

¹⁴ See CSP Appendix V.

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- ¹⁵ Ophthalmology toxicity evaluation: eye exam with emphasis on corneal, lens and retinal changes. In children with orbital PN, the intraocular pressure was measured at baseline and subsequently, if feasible.
- ¹⁶ Patients of childbearing potential, as defined by institutional standards (NIH: ≥ 9 years or those showing pubertal development), required a negative pregnancy test prior to starting treatment and prior to every radiographic scan (prior to Cycles 5, 9, 13, 17, 21 and 25, and then after every 6 cycles). Patients of childbearing potential had to use an acceptable method of birth control; abstinence was an acceptable method of birth control.
- ¹⁷ Adherence questionnaire (see CSP Appendix XVI) completed if the diary review and pill count revealed an unexplained discrepancy $>20\%$.
- ¹⁸ See CSP Appendix XIV.
- ¹⁹ See CSP Appendix XI.
- ²⁰ For patients with lower extremity or airway PN, or patients with cord compression; see CSP Appendix IXA for endurance evaluation (6-minute walk test).
- ²¹ See CSP Appendix VII, Appendix VIII, Appendix IX and Appendix X for functional evaluations.
- ²² Patients with PN affecting motor function had strength, range of motion (also known as quantitative muscle testing; see CSP Appendix IX) and a PRO measure (PROMIS, which is a motor function measure scale; see CSP Appendix XI). Patients with PN in the lumbosacral plexus or below (i.e., lower extremity) underwent leg length testing (see CSP Appendix IXD). Patients with upper extremity PN or cervical/upper thoracic cord compression underwent Grooved Pegboard testing (see CSP Appendix IXE).
- ²³ Patients with a tracheostomy were not required to perform PFTs.
- ²⁴ Patients with PN affecting their airway had the sleep study obtained at baseline. If normal at baseline, it was repeated prior to Cycle 13 and then only as clinically indicated for monitoring. If abnormal at baseline, it was obtained prior to Cycles 5, 9, 13 and then annually. Patients who had a tracheostomy that bypassed the airway obstruction caused by the PN did not require sleep study evaluations. Patients who required CPAP or BiPAP support had a baseline sleep study at their home settings.
- ²⁵ Only patients enrolled at the NCI (See CSP Appendix IIC). Patients with abnormal BMD had a repeat DEXA scan at 1 year, and then as clinically indicated.
- ²⁶ See CSP Appendix XII for timing of PK samples. Differences in timing of the PK sample from the target time were recorded on the PK sheet but not reported as protocol deviations.
- ²⁷ See CSP Appendix XIII for pharmacodynamic studies: cytokines and peripheral blood progenitor cells. If samples for endothelial progenitor cells could not be obtained in time to be delivered, due to patients starting treatment on a Friday or prior to a holiday, this was noted but not reported as protocol deviations.
- ²⁸ See CSP Appendix XIIC for phospho-ERK assay instructions. Differences in timing of the pharmacodynamic sample from the target time were recorded on the pharmacodynamic sheet but not reported as protocol deviations.
- Note: The yearly growth assessment required integration of information including height measurements, puberty staging and bone age (if clinically indicated), which were plotted onto growth charts. Children with impaired growth velocity were referred to a pediatric endocrinologist, as clinically indicated, for evaluation and were followed until they reached final adult height.
- ALT Alanine aminotransferase; AST Aspartate aminotransferase; BiPAP Bilevel positive airway pressure; BMD Bone mineral density; BP Blood pressure; BSA Body surface area; BUN Blood urea nitrogen; CBC Complete blood count; CPAP Continuous positive airway pressure; CPK Creatine phosphokinase; CSP Clinical Study Protocol; DEXA Dual-energy X-ray absorptiometry; ECG Electrocardiogram; ECHO Echocardiogram; ERK Extracellular signal related kinase; LVEF Left ventricular ejection fraction; MRI Magnetic resonance imaging; NCI National Cancer Institute; NIH National Institute of Health; PFT Pulmonary function test; PI Principal investigator; PK Pharmacokinetic(s); PN Plexiform neurofibromas; POB Pediatric Oncology Branch; PRO Patient-reported outcomes; PROMIS Patient-reported outcomes measurement information system; RMQ Responsibility for Medication Questionnaire.

The FDA's Assessment:

The FDA agrees with description of SPRINT Phase II Stratum 1 trial design presented in this section.

The FDA considers the external control data to be supportive in a descriptive manner. Therefore, the data from the NCI POB NF1 Natural History Study and the placebo arm of Tipifarnib Study 01-C-0222 were not independently confirmed and will not be included in FDA's assessment of the efficacy results for SPRINT Phase II Stratum 1.

Study Endpoints

The Applicant's Description:

ORR

The primary outcome variable pre-specified in the protocol was objective response rate (ORR).

The target PN was selected by the assessing investigator as the most clinically relevant PN, amenable to volumetric MRI analysis, to follow during the study. Tumor response was evaluated at re-staging visits prior to Cycles 5, 9, 13, 17, 21, 25, and then after every 6 cycles until permanent discontinuation of selumetinib and response was classified as summarized in Table 20.

Table 20 SPRINT Phase II Stratum 1: Classification of PN Response

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

The target PN was selected by the assessing investigator as the most clinically relevant PN to follow during the study.

CR Complete response; PN Plexiform neurofibroma(s); PR Partial response.

Following FDA request, a retrospective independent central review (ICR) of the SPRINT Phase II Stratum 1 volumetric MRI assessments was conducted by [REDACTED] ^{(b) (4)} as a sensitivity analysis.

Duration of Response, PFS, TTP and Time to Response

Additional secondary endpoints in SPRINT Phase II Stratum 1 were duration of response (DoR), tumor volume changes, PFS (including comparison with PFS in placebo arm of tipifarnib Study 01-C-0222), TTP and time to response (TTR). These were based on the NCI POB centrally read volumetric MRI of target PN, according to Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria.

Clinical Outcome Assessments (COAs)

A range of COAs presented below were used to assess the clinical benefit of selumetinib:

- Pain: Numeric rating scale-11 (NRS-11) and pain interference index (PII)
- Motor function: Strength manual muscle test (MMT), ROM, patient-reported outcomes measurement information system (PROMIS) mobility and upper extremity, grooved pegboard, grip strength, and leg length discrepancy
- Airway function: Apnoea-Hypopnoea Index (AHI, sleep study), forced expiratory volume in 1 second (FEV1), forced expiratory volume in 0.75 seconds (FEV0.75), and R20 (resistance)
- Bowel/bladder function: Dysfunctional voiding questionnaire (DVQ)
- Visual function: visual acuity, amount of exophthalmos
- Disfigurement: standardized photography at each re-staging visit
- Global Impression of Change (GIC)
- HRQoL: Pediatric Quality of Life Inventory (PedsQL)
- Other: 6-minute walk test (6MWT)

Pain (NRS-11 and PII) evaluations, functional patient-reported outcome (PRO) assessments and PedsQL were done at: pre-study; prior to Cycles 3, 5, 9, and 13, then every 12 cycles; and at the end of selumetinib treatment, if possible.

Functional evaluations, including 6MWT were done at: pre-study; prior to Cycles 5, 9, and 13, then every 12 cycles; and at the end of selumetinib treatment, if possible.

Additional Analyses

As specified in the statistical analysis plan (SAP), additional analyses included external comparison of growth data and PFS with data from the NCI POB NF1 Natural History study.

The FDA's Assessment:

The FDA agrees that the study endpoints presented in this section were specified in the protocol and/or in the statistical analysis plan (SAP). We have the following comments:

1. The FDA agreed with plan to assess ORR by both the NCI POB central analysis and by an external independent central review committee. In general, the FDA requests confirmation

of investigator assessed ORR and DOR with independent central review for regulatory assessment in the context of a single-arm trial.

2. The open-label trial design limits interpretability of the COA endpoints because patient's (or parent/caregiver's) knowledge of treatment assignment may lead to systematic overestimation or underestimation of treatment effect which is currently unknown. Other challenges to interpretation of these endpoints include lack of a comparator treatment arm, small sample size, and potential instrument limitations.
3. The FDA considers time-to-event endpoints, such as PFS, TTP, TTR, to be uninterpretable in a single-arm trial. The analyses of these endpoints were considered exploratory and were not verified by the FDA.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP was agreed upon and finalized prior to the conduct of any efficacy analysis and locking of the database. Ad hoc analyses were added following the database lock to support the clinical interpretation.

Efficacy Analysis

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

Primary Endpoint

The primary efficacy endpoint of the study was ORR based on the NCI POB central analysis of volumetric MRI of target PN. ORR was defined as the percentage of patients with complete response (CR) or confirmed partial response (PR; defined as target PN decrease $\geq 20\%$ compared with baseline; confirmed when observed again within 3 to 6 months), per REiNS criteria, and was based on patients who received at least 1 dose of selumetinib (i.e., FAS).

FAS patients with no imaging assessments were counted as non-responders. ORR was presented with corresponding 2-sided exact 95% CIs based on the Clopper-Pearson method (Clopper and Pearson 1934).

A sensitivity analysis of the ORR based on the ICR of the imaging data was also performed. Supplementary analyses were performed to derive ORR based on all available volumetric MRI scans.

Secondary Endpoints

DoR

DoR was defined as the time from the pre-cycle volumetric MRI assessment of the first documented response (subsequently confirmed) until the pre-cycle volumetric MRI assessment of documented progression on treatment or death in the absence of disease progression. The Kaplan-Meier method was used to calculate median DoR and 95% CI and the number and percentage of patients remaining in response for at least 4, 8, 12, 16, 20, and 24 cycles. Only patients who had a CR or confirmed PR were included in this analysis.

Two pre-specified sensitivity analyses of the DoR were also performed:

- The DoR based on the ICRs was derived using the same statistical method as for the analysis of DoR based on the central NCI POB review of the 3D volumetric MRI images on target lesions only.
- The DoR based on the actual dates of the NCI POB-based volumetric MRI assessments or death (if any) was also derived to assess the impact of dose interruptions on the DoR.

A supplementary analysis was performed to derive DoR based on all available volumetric MRI scans.

PFS, TTP, TTR

PFS was defined as the time from study treatment/placebo initiation until the pre-cycle volumetric MRI assessment/date of objective disease progression on treatment/placebo or death (by any cause in the absence of progression) for SPRINT Phase II Stratum 1/placebo arm of tipifarnib Study 01-C-0222, respectively. Patients not known to have progressed at the time of analysis are censored at the last evaluable on-treatment pre-cycle volumetric MRI assessment.

TTP was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of objective disease progression on treatment. Patients not known to have progressed at the time of analysis are censored at the last evaluable on-treatment pre-cycle volumetric MRI assessment.

TTR was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of the first documentation of CR or a subsequently confirmed PR. The pre-cycle volumetric MRI assessment of the first documented response was to coincide with that used for the DoR endpoint. The TTR time was derived based on scheduled pre-cycle volumetric MRIs. Only patients who had achieved a CR or a confirmed PR were evaluated for TTR.

Kaplan-Meier curves were produced for

- PFS, including ad hoc PFS analysis for SPRINT Phase I and comparison of PFS to the placebo arm of the tipifarnib study [01-C-0222]
- TTP, including TTP for SPRINT Phase I and comparison of TTP to the placebo arm of the tipifarnib study [01-C-0222]
- TTR

The median PFS, TTP and TTR (calculated from the corresponding Kaplan Meier plot, with 95% CIs) were also summarized.

A supplementary analysis was performed to derive PFS based on all available volumetric MRI scans for SPRINT Phase II Stratum 1 and SPRINT Phase I.

Inter-reader Variability

The margins of error for target PN volume at baseline and for percentage change from baseline were assessed using the intraclass correlation coefficient (ICC), which compared the assessment of 2 independent readers from (b) (4) on 10 randomly chosen patients. Mixed models were used to estimate the inter-reader and inter-subject standard deviations (SDs).

Clinical Outcome Assessments

The primary analysis of the COAs was based on the descriptive statistics and mixed model repeated measures (MMRM) models that summarize the changes over time on key COAs. In addition, supportive analyses using clinically meaningful thresholds (CMT) were conducted to help with interpretation of clinical benefit. Thresholds for meaningful change were estimated using both distribution (one-half SD) and anchor-based (with GIC as the anchor) approaches. Whenever available, thresholds from published literature were also used.

In order to characterize the relationship between the effect of selumetinib on key PRO and functional outcomes and target PN volume reduction, the correlation and association between changes in PROs and functional outcomes and percent target PN volume change from baseline to pre-Cycle 13 was also explored using scatterplots and Spearman rank correlation coefficients (Cohen 1998).

In addition, the association between longitudinal changes in key PROs and functional outcomes and percentage change from baseline in target PN volume was evaluated using a mixed model analysis.

Additional Analysis

A comparison of PN growth rates and PFS of SPRINT Phase II Stratum 1 to the NCI POB NF1 Natural History study age-matched population was performed. The analysis was done for

2 time periods: all available follow-up data or aligned to the maximum follow-up duration in SPRINT Phase II Stratum 1.

For the Natural History study, crude PN growth rate was defined as the percent change in PN volume from the first to the last volumetric MRI assessment over time period in years, where time period was defined from the first to the last available volumetric MRI assessment or last volumetric MRI assessment date prior to the first use of a MEK inhibitor (including selumetinib).

For SPRINT Phase II Stratum 1, crude PN growth rate was defined as the percent change in target PN volume from the baseline volumetric MRI to the last volumetric MRI assessment over time period in years, where time period was defined from the baseline volumetric MRI assessment date to the last evaluable assessment date up to DCO or treatment discontinuation (whichever occurred first).

Adjusted estimates of growth rate were derived from a random coefficient mixed model for the Natural History study and a repeated measure mixed model for the SPRINT Phase II Stratum 1.

In the Natural History study, PFS was defined as the time from the first volumetric MRI assessment to the date of documented progression or death in the absence of disease progression.

Individual patient reviews

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

SAP Amendments

Table 21 SPRINT Phase II Stratum 1: SAP Amendments Summary

SAP Version	Date	Revisions
Edition 1.0	1 March 2017	Draft version to describe analysis plan for Phase I only
Edition 2.0	21 March 2017	Draft version to include analysis plan for Phase II
Edition 3.0	24 July 2017	First version submitted to FDA
Edition 4.0	7 August 2018	• Definitions of efficacy endpoints were added and analysis further described • ICR analysis was added, following FDA request • COAs section was updated, following FDA request, to include compliance, clinically meaningful threshold, analysis of change from baseline analysis using MMRM models and correlation analysis between tumor volumes and COAs
Edition 5.0	21 January 2019	New section to estimate the margin of error for tumor measurements by inter-reader variability was added COAs section was updated to include further summaries and figures following FDA request.

COA Clinical Outcome Assessment; FDA Food and Drug Administration; ICR Independent central review; MMRM Mixed model repeated measures; SAP Statistical analysis plan.

The FDA's Assessment:

The FDA agrees with the definition of the primary endpoint, primary analysis population, and statistical method used for the analysis of the primary endpoint for Study SPRINT Phase II Stratum 1.

Protocol Amendments

The Applicant’s Description:

Table 22 SPRINT Phase II Stratum 1: Protocol Amendments Summary

Number (Date of Internal Approval)	Key Details of Amendment	Reason for Amendment
Protocol Amendment J (28 Dec 2015)	Screening evaluations were added. Measurement of IOP for children with orbital PN (if feasible) was added to screening and on-study evaluations.	Screening and on-study evaluations were added/amended to allow for accurate safety assessments.
	Secondary objective and related assessments added.	At the request of the EMA and AstraZeneca, the following SPRINT Phase II secondary objective was added: To evaluate the effect of selumetinib on ERK phosphorylation in PBMC.
	Definition for “increase in PN volume” changed.	Clarification of the definition of increase in PN volume after a dose reduction, to allow patients who demonstrated an increase in PN volume after a dose reduction to return to the dosing level prior to dose reduction.
	The schedule for blood sampling for PK on-study evaluations was updated to inform that the steady state sample could be collected prior to Cycle 2 or Cycle 3.	To allow flexibility to enhance compliance.
	Timelines for entering data onto eCRFs changed.	To allow flexibility to enhance compliance.
Protocol Amendment K (26 Apr 2016)	CAEPR and list of AEs reported on selumetinib studies for which there is insufficient evidence to suggest that there was a reasonable possibility that selumetinib caused the AE were updated.	A request for rapid amendment by CTEP.
Protocol Amendment L (10 Aug 2016)	Guidelines for treatment modifications were updated.	To allow patients who have previously dose reduced (BID continuous daily dosing to BID 5x days dosing) due to a DLT to resume continuous daily dosing at the same dose level, if they have continued PN volume increase.
	Criteria for removal from protocol therapy was updated.	For completeness of safety reporting.

Table 22 SPRINT Phase II Stratum 1: Protocol Amendments Summary

Number (Date of Internal Approval)	Key Details of Amendment	Reason for Amendment
	Screening failure was added to the list of criteria leading to removal from the study.	The off-study criteria were updated to allow screen failures to be removed from the study.
	Process of obtaining re-consent via telephone and of obtaining informed consent from non-English-speaking patients was added.	To allow informed consent to be obtained to fulfil Inclusion Criterion 11.
Protocol Amendment M (28 Sept 2016)	Criteria for starting subsequent treatment cycles was updated.	To allow patients who experienced $\geq$ Grade 3 weight gain to re-start at a reduced dose if the weight gain resolved to $\leq$ Grade 2.
	Update to Inclusion Criterion 9, Cardiac function.	To account for institutional differences.
	Update to screening evaluations and Exclusion Criterion 1.	To allow institutional standards to be used to determine the age at which female patients must have a pregnancy test.
	Update to Exclusion Criterion 12, concurrent therapies, and the Patient Drug Information Handout and Wallet Card.	To ensure safety and compliance.
	Updates to screening evaluations to be obtained.	The timeframe for the screening MRI scan was changed from within 4-6 weeks to within 6 weeks of enrolment on study.
	Clarification for when doses could be increased to account for changes in body surface area.	Drug administration was clarified.
	Clarification of treatment modifications in the event of an AE.	The following statement was added: 'Selumetinib doses may be held as needed by the study team to help elucidate if an adverse event is possibly related to drug.'
	Language was updated regarding protocol deviations and scheduling.	To allow flexibility to enhance compliance.

Table 22 SPRINT Phase II Stratum 1: Protocol Amendments Summary

Number (Date of Internal Approval)	Key Details of Amendment	Reason for Amendment
	CSP Appendix IV form to capture photography data was updated.	The ‘Photography of Visible PN Phase II’ form was updated to include a video section.
	CSP Appendix VIII (Airway function) updated.	CSP Appendix VIII updated to state patients who had a tracheostomy which bypassed the airway obstruction caused by the PN did not require sleep study evaluations. Patients who required CPAP or BiPAP support were to have a baseline sleep study at their home settings.
	CSP Appendix VIII (Airway function) updated.	Updated to state that patients with a tracheostomy were not required to perform pulmonary function tests.
Protocol Amendment N (18 June 2018)	CAEPR, SPEER grades and list of risks/AEs reported on selumetinib studies for which there is insufficient evidence to suggest that there was a reasonable possibility that selumetinib caused the AE were updated.	A request for rapid amendment by CTEP.
Protocol Amendment O (14 November 2018)	The frequency of functional evaluations for patients enrolled on Phase II Stratum 2 were reduced	Since Stratum 2 patients were enrolled with non-clinically significant or no functional deficits we do not anticipate significant changes in the outcomes of these evaluations over time.
	Clarification was added that a determination should be made whether weight gain was due to an AE or a desirable effect	Clarification
	Clarification that the volumetric MRI used to determine re-treatment eligibility should be used as the new baseline scan for subsequent volumetric comparisons instead of the baseline volumetric MRI at enrolment.	Clarification
	Update to sections for criteria for removal from protocol therapy and off-study criteria	To allow patients to stay on treatment for longer and derive benefit

Table 22 SPRINT Phase II Stratum 1: Protocol Amendments Summary

Number (Date of Internal Approval)	Key Details of Amendment	Reason for Amendment
Protocol Amendment P (14 January 2019)	References to the (b) (4)	Due to recent organisational changes
	CAEPR was updated.	A request for rapid amendment by CTEP.

All protocol amendments were reviewed by AstraZeneca before being submitted to a regulatory authority and/or an IRB.

AE Adverse event; BID Twice daily; BiPAP Bilevel positive airway pressure; C3D Cancer Central Clinical Database; CAEPR Comprehensive Adverse Event and Potential Risks; CPAP Continuous positive airway pressure; CRF Case report form; CSP Clinical study protocol; CTEP Cancer Therapy evaluation Programme; DLT Dose-limiting toxicity; EMA European Medicines Agency; ERK Extracellular signal related kinase; IOP Intraocular pressure; IRB Institutional Review Board; MRI Magnetic resonance imaging; NCI National Cancer Institute; NIH National Institute of Health; PBMC Peripheral blood mononuclear cells; PK Pharmacokinetic(s); PN Plexiform neurofibroma; QTc Corrected QT interval; QTcF QT interval corrected using Fridericia’s correction formula; SPEER Specific Protocol Exceptions to Expedited Reporting.

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The FDA's Assessment:

The FDA agrees with the description of protocol amendments presented in this section.

8.1.2. **SPRINT Phase II Stratum 1 Study Results**

Compliance with Good Clinical Practices

The Applicant's Position:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice (GCP), applicable regulatory requirements and relevant CTEP and study centre guidelines.

The FDA's Assessment:

The FDA acknowledges the Applicant's statement of compliance with GCP. The FDA also refers to the following statement in Module 2.5, *Clinical Overview*: "AstraZeneca procedures, internal quality control measures and audit programmes provide reassurance that the clinical study program was carried out in accordance with Good Clinical Practice, as documented by the International Council for Harmonization."

Financial Disclosure

The Applicant's Position:

See Section 19.2.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a list of all investigators who participated in SPRINT who have financial disclosure forms held by CTEP. According to the Applicant, CTEP queried investigators for possible financial conflict of interest for NCI Protocol 8799 (SPRINT), and none reported any financial conflicts of interest with AstraZeneca or Merck. The Applicant also submitted certification that AZ acted with due diligence but was unable to obtain the missing financial disclosure information (option 3 on FORM FDA 3454) for three investigators due to the individual no longer being employed at the clinical trial site.

Patient Disposition

Data:

Table 23 SPRINT Phase II Stratum I: Patient Disposition (All Patients)

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

¹ Informed consent received.

² Percentages are calculated from number of patients who were assigned to selumetinib.

³ Percentages are calculated from number of patients who received selumetinib.

BID Twice daily; CSR Clinical study report.

Source: Table 11.1.1, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

The Applicant's Position:

In SPRINT Phase II Stratum 1, 50 patients were enrolled and received at least 1 dose of selumetinib (Table 23). In total, 16 patients discontinued selumetinib; the reasons were: AE (6 patients), disease progression (3 patients), investigator discretion (3 patients), treatment period completed (2 patients), patient not willing to continue treatment (1 patient) and severe non-compliance to protocol (1 patient).

Four patients who discontinued treatment also terminated the study; the reasons were voluntary discontinuation by patient (2 patients), lost to follow-up (1 patient) and other (1 patient). There were no deaths during SPRINT Phase II Stratum 1.

The FDA's Assessment:

The FDA agrees with the results for the patient disposition of SPRINT Phase II Stratum 1 presented in this section.

Protocol Violations/Deviations

Data:

See the Applicant's position below.

The Applicant's Position:

In SPRINT Phase II Stratum 1, 2 (4.0%) patients had important protocol deviations; 1 patient did not comply with protocol requirements (return of diary and missed evaluations) and 1 patient did not repeat an ECHO for a Grade 2 AE of left ventricular ejection fraction (LVEF) within the protocol specified time. Neither of these important deviations influenced the overall efficacy conclusions.

The FDA's Assessment:

The SPRINT protocol defined protocol deviation as "any change, divergence, or departure from the IRB-approved research protocol." The protocol additionally states that "any change or divergence in the scheduling or conduct of examinations, tests and scans or sporadic missing vital signs or laboratory tests described in this protocol will NOT be considered a protocol deviation and will not require reporting to the (b) (4) or FDA unless it meets the definition of unanticipated problem or serious non-compliance." Therefore, isolated missed laboratory or time PK assessments and missed selumetinib doses were documented but not reported as deviations. Unanticipated problems were reported as deviations and included events that were unexpected in terms of nature, severity or frequency in relation to research risks and the characteristics of the study population, or that were related to participation in the research, or that suggested that the research trial put the patients or others at greater risk of harm than previously known or recognized.

The FDA agrees with the Applicant's description of the two events that were classified as protocol deviations in the SPRINT Phase II Stratum 1 cohort. The first patient was removed on Day 64 for noncompliance. The second patient had a Grade 2 AE of decreased LVEF pre-Cycle 9; however, the ECHO was not repeated 3 to 6 weeks later per protocol. It was rather repeated 16 weeks later. The ECHO showed LVEF improvement at this later assessment.

Two additional protocol deviations occurred during SPRINT Phase 1. In both cases, the patients had been dose-reduced for AEs and the subsequent tumor evaluations demonstrated regrowth (not meeting threshold for PD). NCI recommended an alternative dose-modification for both patients (full dose for 5 days on/2 days off) in an effort to more effectively block the MEK pathway. These dose modifications were discussed with CTEP and the IRB however the required protocol amendments were not submitted.

Table of Demographic Characteristics

Data:

Table 24 SPRINT Phase II Stratum 1: Demographic and Patient Characteristics (FAS)

		Selumetinib 25 mg/m ² BID (N=50)
Age, years ¹	n	50
	Mean (SD)	10.3 (3.92)
	Median (min, max)	10.2 (3.5-17.4)
Sex, n (%)	Male	30 (60.0)
	Female	20 (40.0)
Race, n (%)	White	42 (84.0)
	Black or African American	4 (8.0)
	Asian	1 (2.0)
	Unknown ²	3 (6.0)
Ethnic group, n (%)	Not Hispanic or Latino	45 (90.0)
	Hispanic or Latino	2 (4.0)
	Unknown ²	2 (4.0)
	Not reported ^b	1 (2.0)
Height, cm	n	50
	Mean (SD)	133.78 (21.023)
	Median (range)	132.78 (100.3-171.2)
Weight, kg	n	50
	Mean (SD)	34.94 (16.484)
	Median (range)	29.55 (15.7-88.7)
BSA, m ²	n	50
	Mean (SD)	1.127 (0.3401)
	Median (range)	1.040 (0.67-1.93)

¹ Age was calculated using the date of informed consent.

² Unknown race refers to patients with race recorded as “Multiple race, specifics unknown”. Patients (b) (6) and (b) (6) had a further description of “African American and Caucasian, no Asian descent”.

BID Twice daily; BSA Body surface area; FAS Full analysis set; Max Maximum; Min Minimum; SD Standard deviation.

Source: Table 11.1.4 and Table 11.1.5; SPRINT Phase II Stratum I, Module 5.3.5.2.

The Applicant’s Position:

In SPRINT Phase II Stratum 1, the majority of patients were White (Table 24) and male and the median age was 10.2 years (range 3.5 to 17.4 years).

External Control Data

Patient demographics were generally similar between SPRINT Phase II Stratum 1 and external control data (the age-matched population of the Natural History study [N=92]) and also the placebo arm of tipifarnib Study 01-C-0222 [n=29]).

The FDA’s Assessment:

The FDA agrees with the demographic data presented in Table 24.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Table 25 SPRINT Phase II Stratum 1: Disease Characteristics (FAS)

Category		Selumetinib 25 mg/m ² BID (N=50)
Target PN volume, mL	Mean (SD)	837.11 (925.011)
	Median (min, max)	487.50 (5.6-3820.0)
Target PN status, n (%)	Progressive	21 (42.0)
	Non-progressive	15 (30.0)
	Unknown	14 (28.0)
Target PN morbidity assignment, n (%) ¹	Disfigurement	44 (88.0)
	Motor dysfunction	33 (66.0)
	Airway	16 (32.0)
	Bowel and/or bladder dysfunction	10 (20.0)
	Orbital (vision)	10 (20.0)
	Other dysfunction	12 (24.0)
Target PN pain present, n (%) ²	Yes	26 (52.0)
	No	22 (44.0)
	Missing	2 (4.0)
Number of target PN morbidities ³	Median (min, max)	3.0 (1-4)

1 Assigned by investigator; patients can have more than one PN-related symptom. The “Other dysfunction” category included patients with PN pain, swallowing, disfigurement and sensory neuropathy.

2 Based on labmatrix data.

3 Does not include symptoms recorded as ‘other’. Pain was included as a PN-related morbidity.

BID Twice daily; CSR Clinical study report; FAS Full analysis set; Max Maximum; Min Minimum; PN Plexiform neurofibroma; SD Standard deviation

Data cut-off: 29 June 2018.

Source: Table 11.1.6, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

The Applicant’s Position:

There were a range of target PN volumes at baseline (median 488 mL; range 5.6 to 3820 mL), which is not unexpected given the variety of locations that these could occur (Table 25). The size of the target PN at baseline is in line with that observed in the pediatric population where they have been documented to reach up to 20% of body weight (Korf 1999; Mautner et al 2008).

In addition, patients were required to have PN-related morbidity at baseline, and the range of target PN volumes demonstrates that small and large PN volumes could result in considerable clinical symptoms. Most patients had some restrictions in physically strenuous activity and

impairment to daily activity at baseline as reflected in the range of Lansky and Karnofsky scales at baseline.

At enrolment, 42.0% patients had a progressive PN (i.e., growth $\geq 20\%$ in the 12 to 15 months prior to enrolment). 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 at baseline illustrating the complex symptom burden from just 1 PN.

Symptoms at Baseline

Forty-seven (94.0%) patients had at least 1 disease-related symptom at baseline and over two-thirds of these patients had either a maximum Grade 2, Grade 3 or Grade 4 symptom at baseline (22 [44.0%], 8 [16.0] and 4 [8.0%] patients, respectively). The Grade 4 symptoms at baseline included: tracheal obstruction extrinsic (2 [4.0%] patients), glaucoma, optic nerve disorder and respiratory failure (each in 1 [2.0%] patient). The most commonly reported symptoms at baseline were muscular weakness (34.0%; Grade 3: 4.0%), limb asymmetry (32.0%; Grade 3: 4.0%), tumour pain (32.0%; Grade 3: 2.0%), joint ROM decreased (26.0%; Grade 3: 8.0%) and scoliosis (26.0%; Grade 3: 6.0%).

Treatment Prior to Study Entry

Overall, 39 (78.0%) patients had received a prior treatment for PN and/or another NF1-related tumor, with most patients having had either a medical therapy or surgery, or both. The 2 most common PN-directed medical treatments (>20% of patients at the ATC level) received by these patients were interferons (including peginterferon) and imatinib. Eighteen patients had received a single medical therapy and the remaining patients had received multiple successive medical therapies. Medical therapies for other NF1 tumors have also been included in this dataset.

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

In addition, 5 patients had target PN affecting the head and/or neck who had PN-related tracheostomy at baseline, 1 of whom had a non-standard tracheostomy and another who was able to be decannulated following treatment.

The disease burden in this population of patients with symptomatic, inoperable PN was reflected in that the majority of patients had already had PN-related medical treatment (62.0%) and/or surgical treatment for PN debulking or resection from various body locations (56.0%) before enrollment. As the patients with inoperable PN only have the treatment option to try and manage their morbidities, many patients were taking concomitant medications for

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morbidity management, including strong analgesic agents, such as pregabalin, oxycodone and amitriptyline.

External Control Data

Patient baseline disease characteristics were generally similar between SPRINT Phase II Stratum 1 and external control data (the age-matched population of the Natural History study [N=92]) and also the placebo arm of tipifarnib Study 01-C-0222 [n=29]).

The FDA's Assessment:

The FDA agrees with the description of demographics and patient characteristics for Study SPRINT Phase II Stratum 1 presented in Table 25.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Data:

See the Applicant's Position below.

The Applicant's Position:

Treatment adherence was measured, using diary review, for Cycles 1 to 12 to improve compliance for the rest of the study (i.e., to allow initiation of adherence interventions, if needed). Overall, treatment adherence over Cycles 1 to 12 was high (mean: 94.13%), with few missed doses.

The FDA's Assessment:

The FDA agrees with the description of adherence described in this section.

Concomitant medication after study entry

Data:

See the Applicant's Position below.

The Applicant's Position:

All patients received at least 1 concomitant medication during the study for treatment of medical conditions or AEs. The most common concomitant medications (>40% of patients) were ondansetron (62.0%), paracetamol (62.0%), mupirocin (52.0%), clindamycin (48.0%), ibuprofen (48.0%), and cefalexin (44.0%). In total, 20 (40.0%) patients received at least 1 medication, which is listed as a medication to avoid, per the CSP, during the study for treatment of medical conditions or AEs; the most common was ketoconazole (18.0%).

During PK collection times, only 2 concomitant medications were used and both were unlikely to affect the PK characterisation of selumetinib. The majority of medications were used topically or for a short duration, which was unlikely to affect the evaluations in this study.

A pain medication survey was collected 1 week prior to enrollment; the most common pain medications ($\geq 10\%$ patients) during enrolment were gabapentin (10 [20.0%] patients) and ibuprofen (5 [10%] patients). Patients were taking a number of different pain medications, including pregabalin, oxycodone and amitriptyline.

The use of concomitant medications was not considered to have impacted the study results.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Table 26 SPRINT Phase II Stratum 1 Confirmed Objective Response Rate: NCI POB Central Analysis (REiNS; FAS)

	Selumetinib 25 mg/m² BID (N=50)
Number (%) of patients with a response ¹	33 (66.0)
95% CI ²	51.2, 78.8

¹ For partial responses, response required consecutive confirmation within 3 to 6 months after the criteria for first response were met.

² Calculated using the Clopper-Pearson exact method for binomial proportions.

Objective response rate was defined as the percentage of patients who received at least 1 dose of selumetinib and had at least 1 complete response or confirmed partial response.

BID Twice daily; CI Confidence interval; CSR Clinical study report; FAS Full analysis set; NCI National Cancer Institute; POB Pediatric Oncology Branch; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.

Source: Table 11.2.1.1.7, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

Table 27 SPRINT Phase II Stratum 1: Confirmed Objective Response Rate by PN Status at Enrolment: NCI POB Central Analysis (REiNS; FAS)

Group	N	Number (%) of Patients with Response ¹	95% CI ²
Selumetinib 25 mg/m ² BID	50	33 (66.0)	51.2, 78.8
Progressive PN ³	21	13 (61.9)	38.4, 81.9
Non-progressive PN ⁴	15	10 (66.7)	38.4, 88.2
Unknown ⁵	14	10 (71.4)	41.9, 91.6

¹ Response required consecutive confirmation within 3 to 6 months after the criteria for first response were met. Partial response = a decrease in the volume of the target PN by 20% or more compared with baseline.

² Calculated using the Clopper-Pearson exact method for binomial proportions.

³ Progressive disease in the 18 months prior to enrolment.

⁴ Not meeting criteria for progressive disease prior to enrolment.

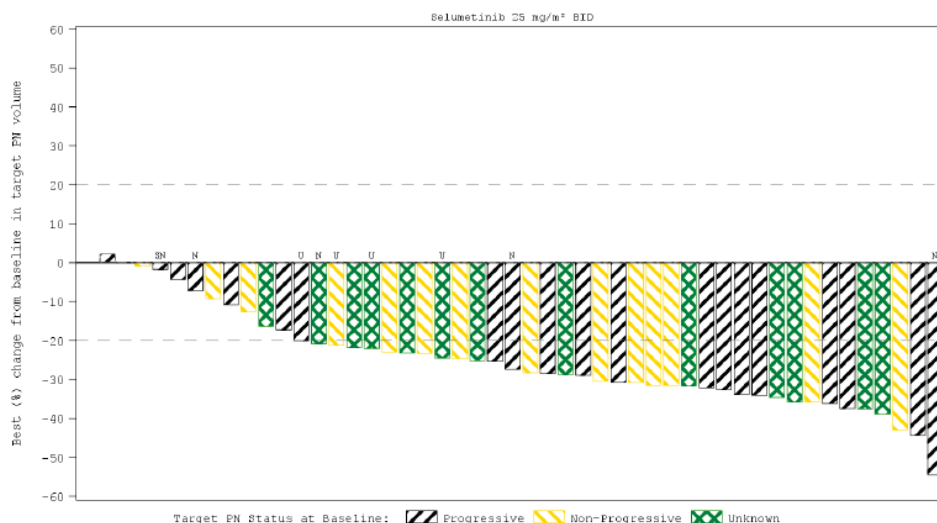
⁵ Determination of progressive/non-progressive PN was not possible based on the prior image available.

BID Twice daily; CI Confidence interval; CSR Clinical study report; FAS Full analysis set; NCI National Cancer Institute; PN Plexiform neurofibroma(s); POB Pediatric Oncology Branch; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.

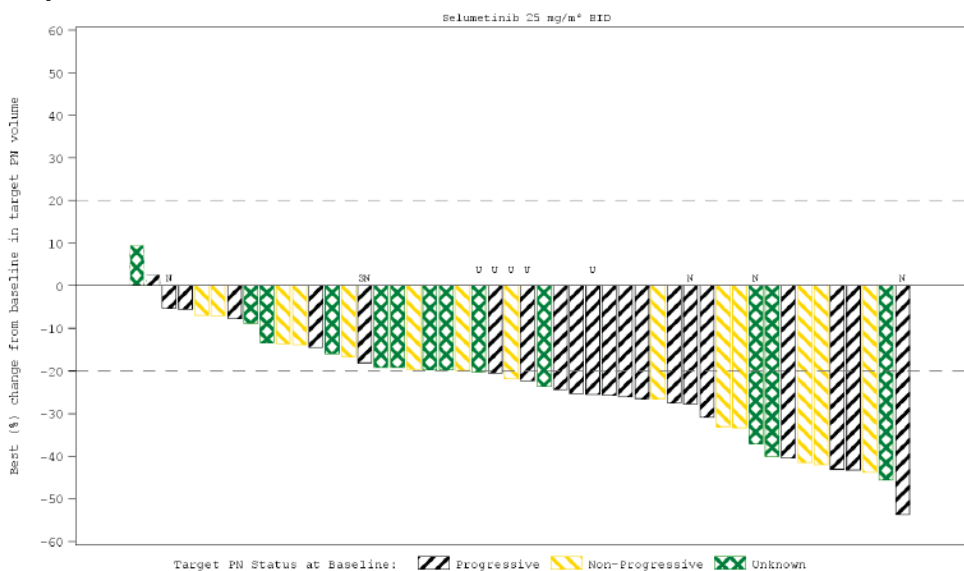
Source: Table 11.2.1.1.10, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

Figure 5 SPRINT Phase II Stratum 1: Best Percentage Change from Baseline in Target PN Volume - Waterfall Plot for NCI POB and ICR Analyses (FAS)

A: NCI POB analysis



B: ICR analysis



Best percentage change in target PN size is the maximum reduction from baseline, or the minimum increase from baseline in the absence of a reduction. Bars not annotated with SN or N represent typical nodular PN.

Includes Patient (b) (6) who only has partial volumes throughout the study.

BID Twice daily; CSR Clinical study report; FA S Full analysis set; ICR Independent central review; PN Plexiform neurofibromas; N Nodular PN; NCI National Cancer Institute; POB Pediatric Oncology Branch; SN Solitary nodular PN; U Unconfirmed response.

Source: Figure 11.2.2.3.2 and 11.2.2.3.4, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

The Applicant's Position:

There was a high ORR of 66.0% (33 of 50 patients by NCI POB central analysis; 95%CI 51.2%, 78.8%) observed in SPRINT Phase II Stratum 1 (Table 26). No patients had a best objective response of disease progression. Supplementary analyses were performed to derive ORR based on all available volumetric MRI scans; ORR by this analysis was 66.0%, i.e., the same as the analysis including only the scheduled scans.

ORR by PN Status at Enrolment: NCI POB Central Analysis

There were similar response rates for patients whose PN were known to be either progressive (i.e., $\geq 20\%$ in the 18 months prior to enrolment; n=21) or non-progressive (n=15) at enrolment, showing that both groups benefited from selumetinib treatment (Table 27). PN status at enrolment appears to be independent from response rate and, therefore, not predictive of selumetinib efficacy.

Sensitivity Analysis: ORR According to ICR

Sensitivity analysis for SPRINT Phase II Stratum 1 based on the ICR, reported an ORR of 44.0% (95%CI: 30.0, 58.7). No patient had a best objective response of progressive disease.

Waterfall plots of the NCI POB central and ICR analyses demonstrate the consistency of results obtained by NCI POB central analysis and ICR (Figure 5), confirming the validity and reproducibility of the NCI POB central analysis.

Both NCI POB central and ICR analyses agreed that:

- No patients with a best objective response of progressive disease
- Only 2 patients had an increase in target PN volume from baseline, but the analyses reported different magnitude in the volume increase of the target PN.

Of note, there were 6 patients assessed by ICR who had target PN shrinkage between -19.2% and -19.9% as their best objective response, which were approaching the PR threshold.

Although ORR by ICR analysis was lower (44.0%, 22 of 50 patients) than that reported by NCI POB central analysis (66.0%, 33 of 50 patients), the differences in categorisations of best objective response between the NCI POB central analysis and the ICR analysis were primarily in assignments of confirmed PR versus stable disease (based on the chosen threshold of reduction of 20% in target PN volume to determine response) as shown in Figure 5.

The FDA's Assessment:

FDA agrees with the results for the ORR presented in this section. There were several patients in the study who had an initial decrease in target PN volume from baseline but had an increase in volume in later visits. The ORR in subgroups based on demographic and clinical characteristics are presented Table 28.

Table 28 SPRINT Phase II Stratum 1: Confirmed Overall Response Rate by Demographic and Clinical Subgroups: ICR Analysis

Age, in years	ORR (95% CI)
≤ 12 (n=33)	52 (34, 69)
> 12 (n=17)	29 (10, 56)
Sex	
Male (n=30)	43 (25, 63)
Female (n=20)	45 (23, 68)
Race	
White (n=42)	48 (32, 64)
Non-White (n=8) ¹	25 (3, 65)
PN status at baseline	
Progressive (n=21)	57 (34, 78)
Non-progressive (n=15)	40 (16, 68)
Unknown (n= 14)	29 (8, 58)

¹Includes 4 patients who are Black or African American

Source: Reviewer generated table using applicant submitted data (ADEFF, ADSL, and ADTU)

Data Quality and Integrity

The Applicant's Position:

Quality of SPRINT Phase II Stratum 1 data was assured through provision of appropriate training for study personnel; this study was conducted at pediatric hospitals leading in patient care. Monitoring was conducted by the (b) (4). Two NCI POB databases were used to collect data for SPRINT Phase II Stratum 1; LabMatrix was used for PN disease evaluation, PROs and functional evaluation data and Cancer Central Clinical Database (C3D) was used for demographic, laboratory, safety (with the exception of dual-energy X-ray absorptiometry [DEXA] data, which were collected in LabMatrix) and PK data. In addition, the Cancer Therapy Evaluation Programme-Adverse Event Reporting System was used for suspected unexpected serious adverse reaction (SUSAR) reporting.

Onsite audits were conducted at all participating sites by (b) (4). In addition, AstraZeneca carried out Quality Assurance GCP audits of SPRINT Phase II Stratum 1 at all 4 sites, to ensure compliance with relevant procedures and to assess the adequacy of quality control measures. Audits, by a (b) (4) operating independently of the study monitors and in accordance with documented policies and procedures, are directed towards all aspects of the clinical study process and its associated documentation.

The FDA's Assessment:

The FDA acknowledges the Applicant's description of trial monitoring and data collection methods, the data quality assurance procedures, and the independent audits that were conducted.

The submission contained all of the required components of the electronic Common Technical Document (eCTD) and was of adequate quality and integrity to allow for review of the clinical trial data supporting the proposed indication. The results from the primary safety and efficacy datasets and the updated safety databases submitted with the 90-Day safety update were reproducible. FDA was able to confirm the Applicant's analyses of the key primary and secondary endpoints discussed in this review.

Multiple information requests were sent to the Applicant during the review cycle. Examples of these were requests to resubmit specific data with a different organization for ease of review, to conduct additional specified safety analyses of the Applicant's global database for selumetinib, to submit additional patient safety narratives, and to provide alternative presentations of efficacy results. The Applicant was able to provide responses to satisfy all FDA information requests.

Efficacy Results – Secondary and other relevant endpoints

Data:

Table 29 SPRINT Phase II Stratum I Progression-free Survival by NCI POB Central Analysis (FAS)

	Selumetinib 25 mg/m² BID (N=50)
Total number of events (progression or death), n (%) ¹	3 (6.0)
Number of progressions, n (%)	3 (6.0)
Number of deaths, n (%)	0
Censored patients, n (%)	47 (94.0)
Median progression-free survival (cycles) ²	NC
Progression-free at Cycle 16 (%), 95% CI ²	100 (NE-NE)
Progression-free at Cycle 24 (%), 95% CI ²	94.7 (80.6-98.7)
Progression-free at Cycle 30 (%), 95% CI ²	88.8 (66.4-96.6)
Progression-free at Cycle 36 (%), 95% CI ²	88.8 (66.4-96.6)
Median follow-up for progression-free survival (cycles) (censored patients only) ³	24.0 (0.0-36.0)

¹ Progression includes deaths in the absence of progression.

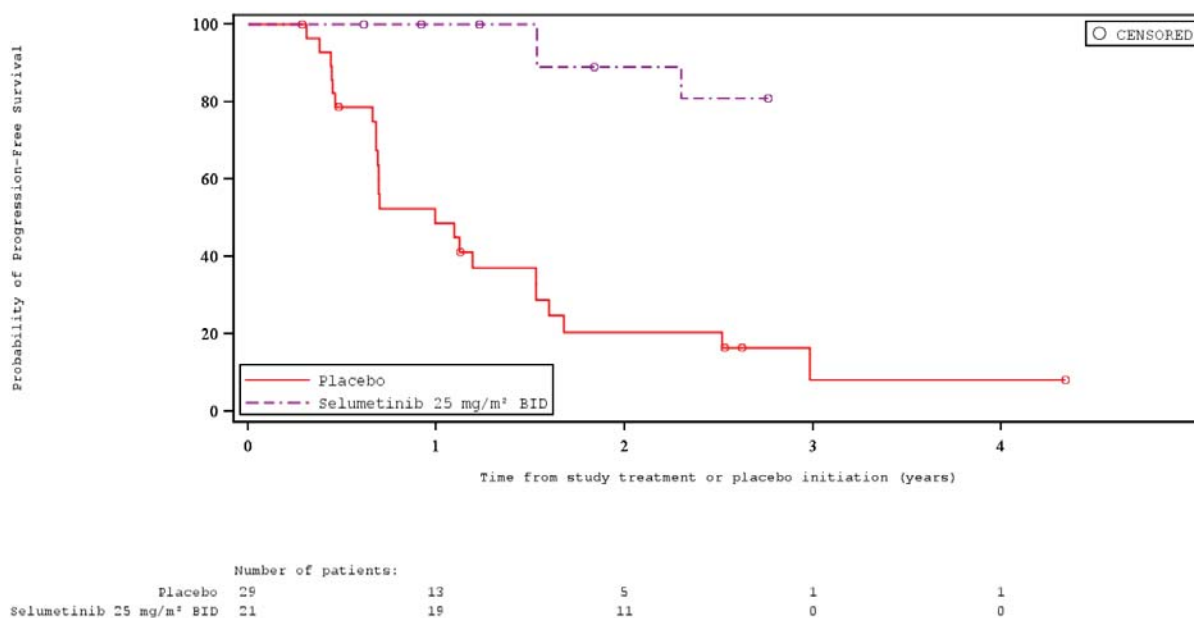
² Calculated using the Kaplan-Meier technique.

³ Calculated as the median time from study treatment initiation to pre-cycle of censoring (last evaluable pre-cycle volumetric MRI assessment known to be non-progression) in censored (not progressed) patients only.

BID Twice daily; CI Confidence interval; FAS Full analysis set; MRI Magnetic resonance imaging; NC Not calculated; NCI National Cancer Institute; NE Not evaluable; POB Pediatric Oncology Branch.

Source: Table 11.2.1.3.1, SPRINT Phase II Stratum 1, Module 5.3.5.2.

Figure 6 SPRINT Phase II Stratum 1: Kaplan-Meier Plot of PFS, Placebo Arm of Tipifarnib Study 01-C-0222: Phase A and SPRINT Phase II Stratum 1 (Progressive PN)



Includes patients with progressive disease in the 18 months prior to enrolment to SPRINT Phase II Stratum 1. PFS is defined as the time from study treatment/placebo initiation until the pre-cycle/date of objective progression or death (by any cause in the absence of progression) for SPRINT Phase II Stratum 1/placebo arm of tipifarnib Study 01-C-0222, respectively.

Patients not known to have progressed or died at the time of analysis are censored at the last evaluable volumetric MRI assessment known to be non-progression.

The values at the base of the figure indicate number of patients at risk.

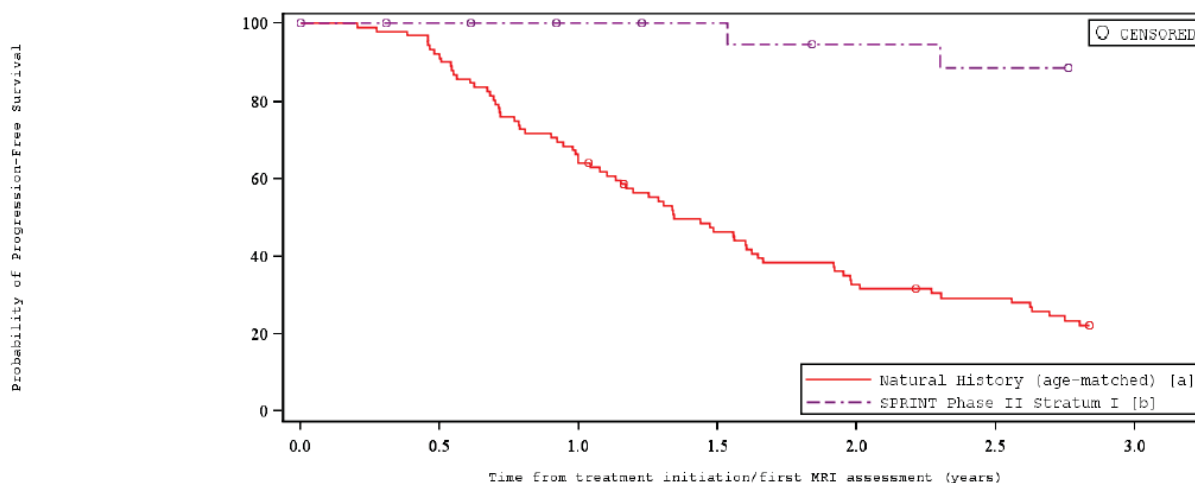
Dots represent censored observations.

SPRINT: PFS in cycles converted to years: Number of cycles×28/365.25.

BID Twice daily; MRI Magnetic resonance imaging; PFS Progression-free survival; POB Pediatric Oncology Branch; PN Plexiform neurofibroma.

Source: Figure 11.2.1.3.13, SPRINT Phase II Stratum 1, Module 5.3.5.2.

Figure 7 SPRINT Phase II Stratum 1: Kaplan-Meier Plot of PFS in Natural History Age-matched Cohort and SPRINT Phase II Stratum 1 Aligned to Maximum Follow-up Duration of SPRINT



	Number of patients:					
Natural History (age-matched) [a]	92	84	59	41	29	25
SPRINT Phase II Stratum I [b]	50	47	41	38	16	5

^a Includes patients who are aged 3 to 18 years with at least 1 volumetric MRI assessment within this age.

^b Includes patients with a baseline volumetric MRI assessment.

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis were censored at the last evaluable volumetric MRI assessment. PFS in cycles converted to years:

No. of cycles * 28/365.25.

Natural History: PFS is defined as the time from first volumetric MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis were censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor, including selumetinib.

The values at the base of the figure indicate number of patients at risk. Dots represent censored observations.

MEK Mitogen-activated protein kinase kinase; MRI Magnetic resonance imaging; PFS Progression-free survival.

Source: Figure 11.2.1.3.10, SPRINT Phase II Stratum 1, Module 5.3.5.2.

Table 30 SPRINT Phase II Stratum 1: Time to Response in Patients with Objective Response: NCI POB Central Analysis (FAS)

	Selumetinib 25 mg/m ² BID (N=50)
Number of patients with an objective response	33
Time to onset of response from first dose (cycles) ^{1,2}	
25th percentile	4.0
Median (95% CI)	8.0 (4.0, 8.0)
75th percentile	12.0
Time to onset of response from first dose, n (%) ²	
≤4 cycles	14 (42.4)
≤8 cycles	24 (72.7)
≤12 cycles	32 (97.0)
≤16 cycles	32 (97.0)
≤24 cycles	33 (100)

¹ Time to response was defined as the time from study treatment initiation until the pre-cycle volumetric MRI assessment of the first documentation of complete response or a subsequently confirmed partial response.

² Calculated using Kaplan-Meier technique. The denominator is the number of patients with objective response. A cycle was defined as 28 days.

BID Twice daily; CI Confidence interval; FAS Full analysis set; MRI Magnetic resonance imaging; NCI National Cancer Institute; POB Pediatric Oncology Branch.

Source: Table 11.2.1.2.1, SPRINT Phase II Stratum 1, Module 5.3.5.2.

The Applicant's Position:

PFS

Of the 50 patients enrolled to SPRINT Phase II Stratum 1, only 3 patients had progressed at the DCO (all 3 patients had progressive PN at enrolment); therefore, the median PFS was not reached and there was a very high probability (94.7% [95% CI: 80.6, 98.7]) of remaining without progressive disease after 2 years in SPRINT Phase II Stratum 1 (Table 29). Two progressions occurred at pre-Cycle 21 and 1 progression occurred at pre-Cycle 31.

Supplementary Analysis

A supplementary analysis was performed to derive PFS based on all available volumetric MRI scans. According to this analysis, 6/50 (12.0%) patients in SPRINT Phase II Stratum 1 progressed, i.e., 3 more patients than were found to have progressed in the main PFS analysis.

External Control: Comparison with the Placebo Arm of Tipifarnib Study 01-C-0222

Results for the efficacy endpoint of PFS from the 29 patients who had progressive PN in placebo arm of tipifarnib Study 01-C-0222 provide an external control for PFS data from SPRINT Phase II Stratum 1.

Based on the last evaluable volumetric MRI assessment in the placebo arm of tipifarnib Study 01-C-0222, 23/29 (79.3%) patients had progressed. In SPRINT Phase II Stratum 1, the subgroup

of patients with progressive PN at enrolment had the probability of remaining without progression at 2 years was 88.9% (95% CI 62.4, 97.1), which was much higher than the 20.6% (95% CI 7.7,37.8) in the placebo arm of tipifarnib Study 01-C-0222 (Figure 6). This analysis was repeated using all 50 patients from SPRINT Phase II Stratum 1 and showed similar results.

External Control: Comparison with the Natural History Study

Figure 7 shows that 76.1% of patients in the Natural History study had disease progression in their target PN compared with 6.0% of patients in SPRINT Phase II Stratum 1, over a 2.8-year period. Median PFS in the Natural History age-matched cohort was 1.3 years (95% CI: 1.1, 1.6) and was not reached in SPRINT Phase II Stratum 1. In SPRINT Phase II Stratum 1, in all patients, the probability of remaining without progression after 2 years was 94.7% (95% CI: 80.6, 98.7) compared with 30.4% (95% CI 21.0, 40.3) in the Natural History study (i.e., no treatment with MEK-inhibitor).

TTP

No deaths were observed in SPRINT Phase II Stratum 1 hence TTP results are the same as of PFS presented above.

TTR

In SPRINT Phase II Stratum 1, in the 33 responders, the majority of patients (24 [72.7%] patients) had a response by 8 cycles from first dose, with almost half (14 [42.2%] patients) having a response detected by 4 cycles from first dose (Table 30).

The FDA's Assessment:

These analyses are exploratory and were not verified by the FDA.

Dose/Dose Response

Data:

Not applicable.

The Applicant's Position:

Not applicable.

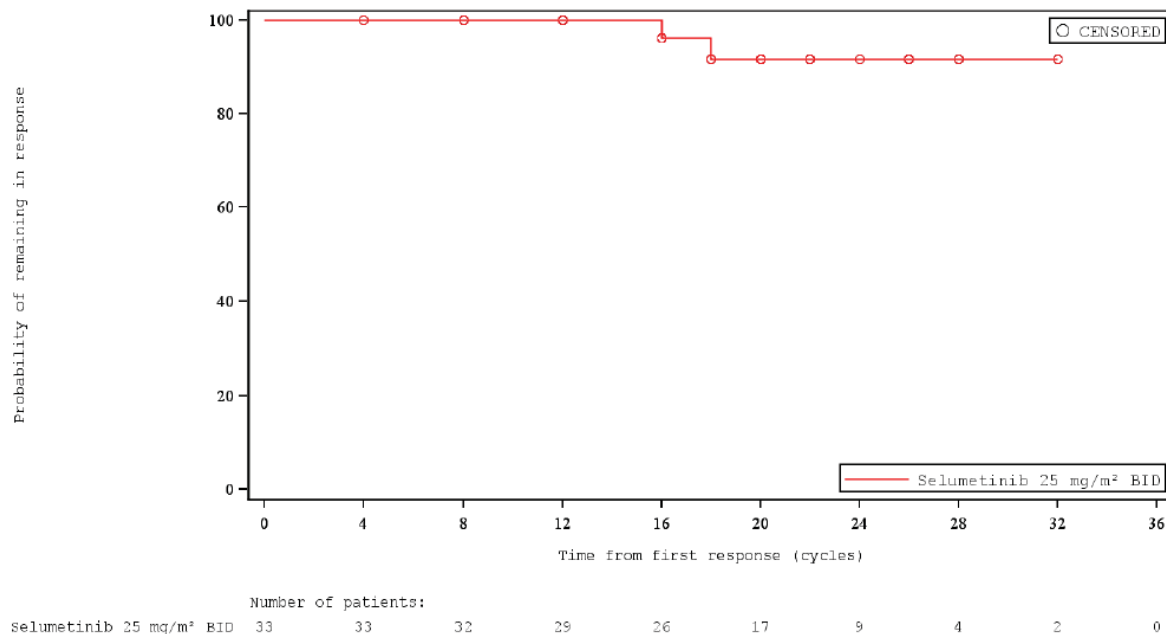
The FDA's Assessment:

Not applicable.

Durability of Response

Data:

Figure 8 SPRINT Phase II Stratum I: Kaplan-Meier Plot of DoR, NCI POB Central Analysis (REiNS; FAS)



DoR was defined as the time from the pre-cycle volumetric MRI assessment of the first documented (which was subsequently confirmed) response until the pre-cycle volumetric MRI assessment of documented progression or death in the absence of disease progression (i.e., pre-cycle volumetric MRI assessment of progression event or censoring – pre-cycle volumetric MRI assessment of first response where each cycle was 28 days). Response required confirmation within 3 to 6 months after the criteria for first response was met.

The values at the base of the figure indicate number of patients at risk.

Dots represent censored observations.

A cycle was defined as 28 days.

BID Twice daily; DoR Duration of response; FAS Full analysis set; MRI Magnetic resonance imaging; NCI National Cancer Institute; POB Pediatric Oncology Branch; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.

Source: Figure 11.2.1.2.2, SPRINT Phase II Stratum 1, Module 5.3.5.2.

Table 31 SPRINT Phase II Stratum 1: Duration of Confirmed Objective Response in Patients with Objective Response: NCI POB Central Analysis (REiNS; FAS)

	Selumetinib 25 mg/m ² BID (N=50)
Number of patients with an objective response	33
Number of patients with an objective response who subsequently progressed	2 ¹
Duration of response from onset of response, cycles ^{2,3}	
25th percentile	NC
Median (95% CI)	NC
75th percentile	NC
Estimate percentage remaining in response ³	
≥12 cycles (95% CI)	100 (NE, NE)
≥16 cycles (95% CI)	96.2 (75.7, 99.4)
≥20 cycles (95% CI)	91.6 (70.1, 97.8)
≥24 cycles (95% CI)	91.6 (70.1, 97.8)
Minimum duration of response, cycles	4.0
Maximum duration of response, cycles	32.0

¹ Progressed after duration of response of 16 and 18 cycles.

² Duration of response was defined as the time from the pre-cycle volumetric MRI assessment of the first documented (which was subsequently confirmed) response until the pre-cycle volumetric MRI assessment of documented progression or death in the absence of disease progression (i.e., pre-cycle volumetric MRI assessment of progression event or censoring – pre-cycle volumetric MRI assessment of first response where each cycle was 28 days). Response required consecutive confirmation within 3 to 6 months after the criteria for first response was met.

³ Calculated using Kaplan-Meier technique. The denominator is the number of patients with objective response. A cycle was defined as 28 days.

BID Twice daily; CI Confidence interval; FAS Full analysis set; MRI Magnetic resonance imaging; NC Not calculated; NCI National Cancer Institute; NE Not evaluable; POB Pediatric Oncology Branch; REiNS Response Evaluation in Neurofibromatosis and Schwannomatosis.

Source: Table 11.2.1.2.1, Appendix 12.2.6.1 and Appendix 12.2.6.2, SPRINT Phase II Stratum 1, Module 5.3.5.2.

The Applicant's Position:

A Kaplan-Meier plot of DoR in SPRINT Phase II Stratum 1 by NCI POB central analysis is presented in Figure 8.

At DCO in SPRINT Phase II Stratum 1 (29 June 2018), 32/33 patients with a response had been followed for at least 12 months from onset of response. Median DoR from onset of response was not reached; at the time of DCO the median follow-up time was 24 cycles (Table 31). Of the 33 responders, the probability of remaining in response after 12 cycles, estimated using the Kaplan-Meier method, was 100%.

Sensitivity Analyses of Duration of Response

Based on actual assessment dates

For the primary analysis, DoR was estimated in cycles with each cycle defined as 28 days in duration. However, this estimation does not account for any delays between cycles or interruptions due to dose modifying toxicities, investigations or other reasons (e.g., surgery). A sensitivity analysis using the actual dates of the volumetric MRI assessments was conducted. This analysis showed that of the 33 responders, the probability of remaining in response after 16 months, estimated using the Kaplan-Meier method was 100%, which was consistent with the primary analysis of DoR.

ICR Assessment

An ICR analysis of DoR was conducted using the same REiNS criteria used by the NCI POB central analysis. Based on the ICR assessment, of the 22 patients with confirmed PR, 7 patients subsequently had disease progression. Median DoR was reached at the last event, 32 cycles after the onset of response, and therefore data are still immature. This was consistent with the primary analysis of DoR, which shows very durable responses.

The FDA's Assessment:

In general, the FDA agrees with the results presented in this section. However, it is difficult to interpret estimates of duration of response measured in time by 28-day cycles. Instead, the FDA calculation of estimates of duration of response considers time as measured by dates. The FDA calculation of the median DOR as assessed by ICR was 21.9 months (95% CI: 17.6, 30.3). The FDA calculation of median DOR as assessed by NCI POB Central Analysis was not reached and the 95% CI was not estimable .)

It is also important to note that, the definition of disease progression in the NCI POB central analysis included non-target lesions and new lesions, whereas the ICR assessments of disease progression were based only on target PN volumes.

Persistence of Effect

Data:

Table 32 SPRINT Phase II Stratum 1: Number (%) Patients Receiving Selumetinib by Month (Safety Analysis Set)

Total exposure (months)	SPRINT Phase II Stratum 1, Selumetinib
	(N=50) n (%)
<12	6 (12.0)
≥12 to ≤24	11 (22.0)
>24 to ≤36	33 (66.0)
>36 to ≤48	0

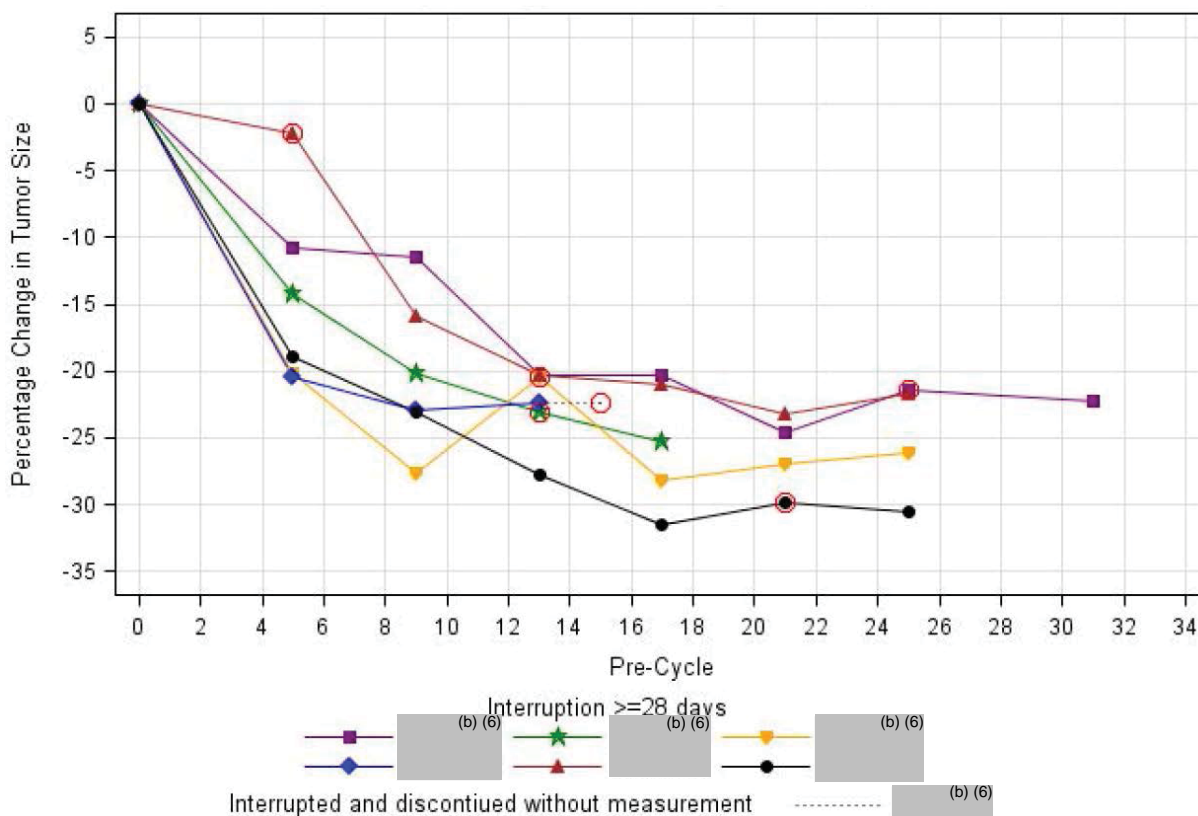
NDA Multi-disciplinary Review and Evaluation NDA 213756
Koselugo (selumetinib)

One month=28 days.

Data cut-off: 29 June 2018

Source: Table 2.7.4.2.1.1 of the ISS Pediatric pool, Module 5.3.5.3.

Figure 9 SPRINT Phase II Stratum 1: Target PN Growth Rate in Patients with No Change in Dose and with Interruptions More than 28 Days between Tumor Assessments (FAS)



FAS Full analysis set; PN Plexiform neurofibroma.

Data cut-off: 29 June 2018.

Source: IEMT015c, Module 5.3.5.3.

The Applicant's Position:

In SPRINT Phase II Stratum 1, the majority of patients (66.0%) remained on selumetinib treatment for at least 24 months (Table 32).

A graphical longitudinal analysis was performed, in which patients with no dose reduction and cumulative interruptions of more than 28 days in between 2 assessments, were plotted. The selection of 28 days was based on 25% of dose not given (1 cycle) during the 4 cycles of treatment between tumor size assessments and it was considered that it might have an impact on disease progression.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

In patients who had no dose reductions and cumulatively had drug interruptions of >28 days between 2 assessments (6/50 patients), there appeared to be an overall trend of PN decrease in all of the patients (Figure 9). At the time of dose interruptions, there appeared to be a slight trend towards lower efficacy compared with the slope of tumor size change before interruptions. However, with limited numbers it is difficult to conclude as such.

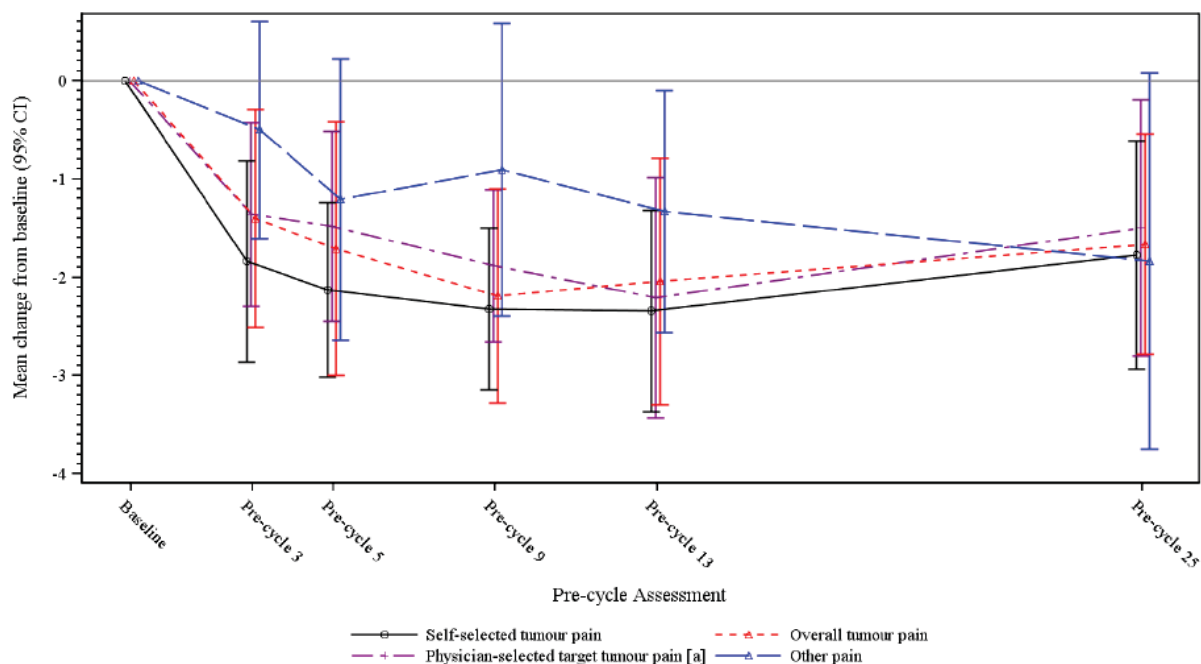
The FDA's Assessment:

These analyses are considered exploratory and were not verified by the FDA. No reliable conclusions can be made based on data from a sample size of six patients.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Figure 10 SPRINT Phase II Stratum I: Mean Change from Baseline of NRS-11 Pain Intensity Scores (FAS)



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

Note: Patients aged 8 to 18 years at enrolment completed self-report measures of the NRS-11 (N=34).

CI Confidence interval; FAS Full analysis set; NRS-11 Numerical Rating Scale-11; PN Plexiform neurofibroma.

Source: Figure 11.2.3.2.5.3, SPRINT Phase II Stratum 1, Module 5.3.5.2.

Table 33 SPRINT Phase II Stratum I: Change from Baseline for NRS-11 Pain Intensity Primary Outcome, MMRM (FAS)

Parameter	Statistic	Selumetinib 25 mg/m ² BID (N=34)				
		Pre-Cycle 3	Pre-Cycle 5	Pre-Cycle 9	Pre-Cycle 13	Pre-Cycle 25
Physician-selected target tumor pain	n	25	25	25	24	18
	Adjusted mean	-1.28	-1.41	-1.83	-2.07	-2.32
	Standard error	0.270	0.345	0.265	0.368	0.474
	95% CI	-1.84, -0.72	-2.13, -0.70	-2.38, -1.28	-2.84, -1.31	-3.34, -1.30
	p-value ¹	<0.001	<0.001	<0.001	<0.001	<0.001

¹ Nominal p-value

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

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

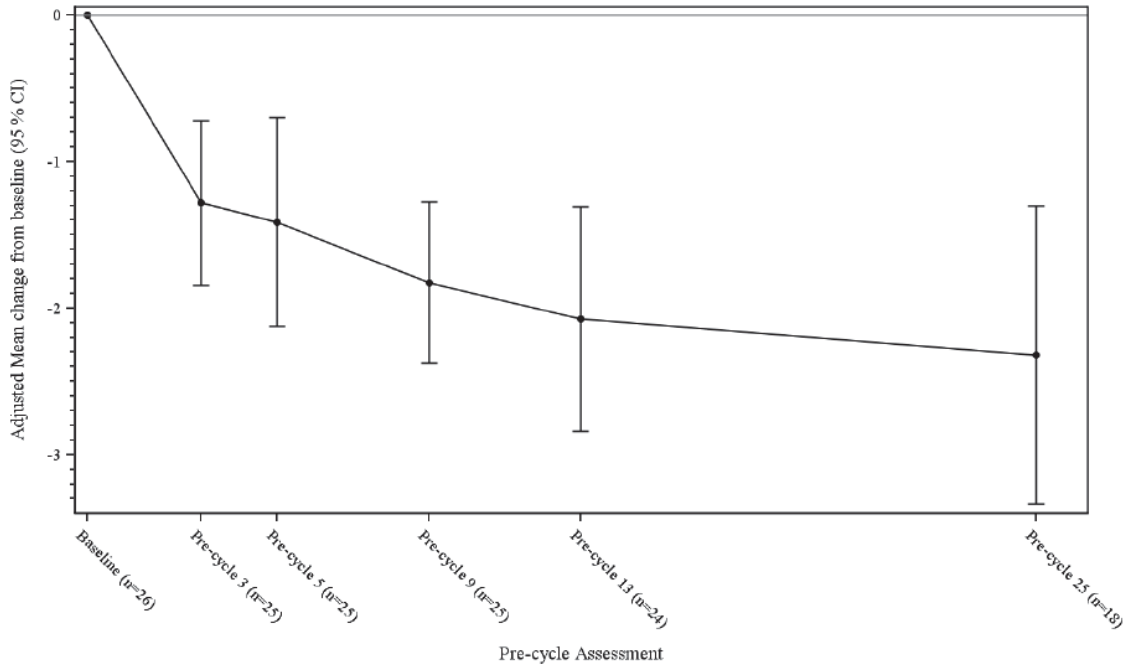
Patients who had their baseline evaluation using an earlier version of the NRS-11, which did not yet include the target tumor item, were considered only if self-selected and target tumor (PN) were the same.

BID Twice daily; CI Confidence interval; FAS Full analysis set; MMRM Mixed model repeated measures;

NRS-11 Numeric rating scale-11; PN Plexiform neurofibroma.

Source: Table 11.2.3.2.5.2, SPRINT Phase II Stratum 1, Module 5.3.5.2.

Figure 11 SPRINT Phase II Stratum I: Adjusted Mean Change from Baseline of NRS-11 Physician-selected Target Tumor Pain Score, MMRM (FAS)

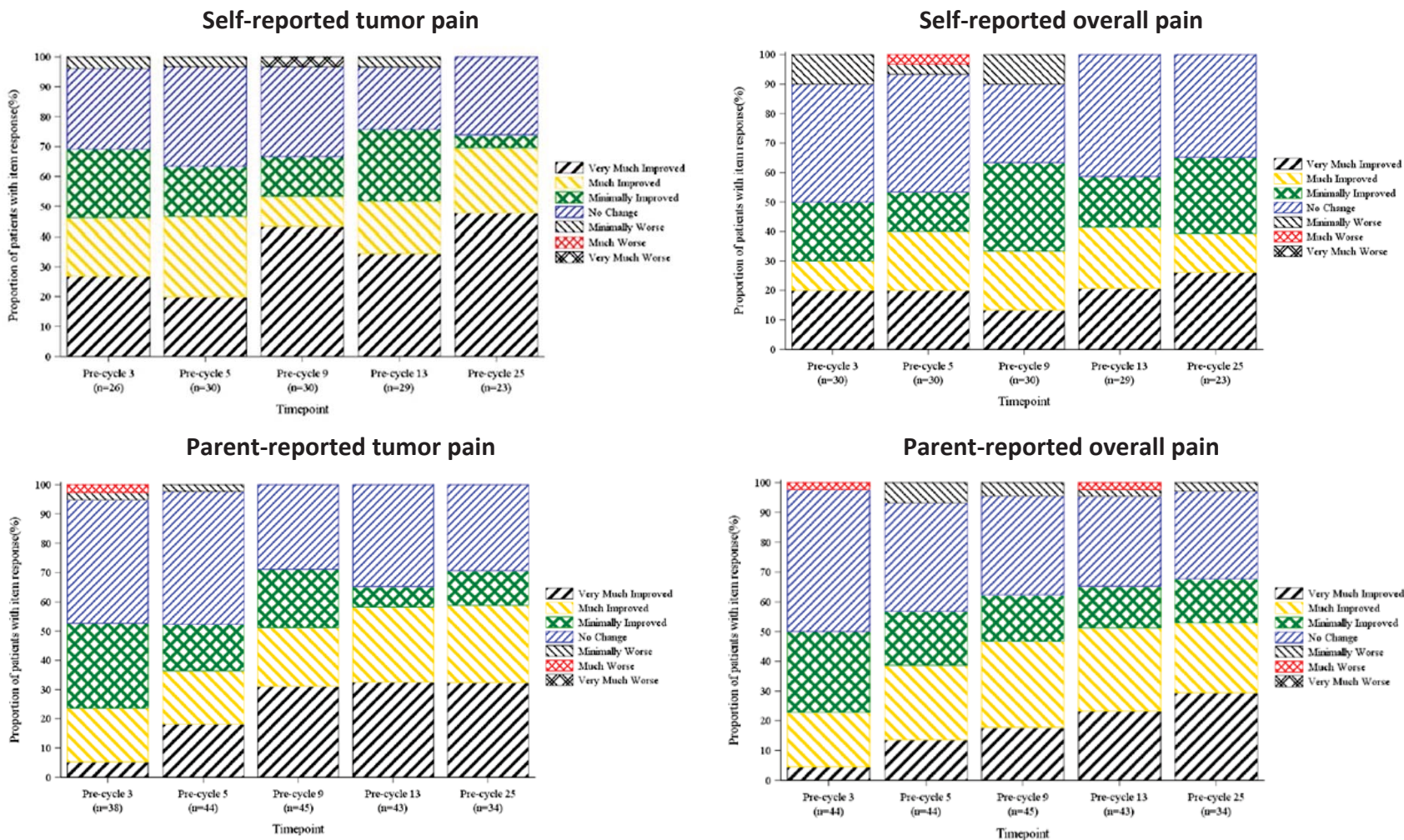


N=34

CI Confidence interval; CSR Clinical study report; FAS Full analysis set; MMRM Mixed model repeated measures; NRS-11 Numeric rating scale-11.

Source: Figure 11.2.3.2.5.6, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

Figure 12 SPRINT Phase II Stratum 1: Distribution of GIC Self-report and Parent-report Item Responses Over Time: Tumor Pain and Overall Pain (FAS)



NDA Multi-disciplinary Review and Evaluation NDA 213756
Koselugo (selumetinib)

Patients aged 8 to 18 years at enrolment were expected to complete self-report measures of the GIC (n=34).

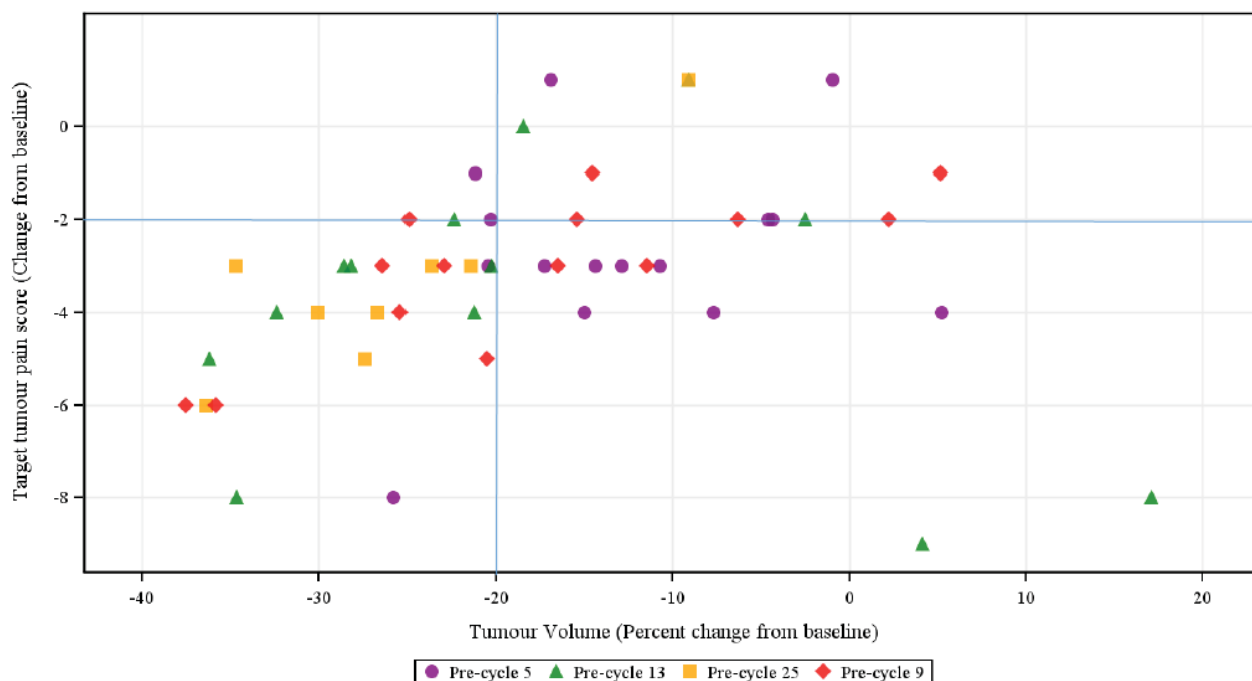
Parents or legal guardians of children aged 5 to 18 years at enrolment expected to complete the parent proxy measures of the GIC (n=48).

CSR Clinical study report; FAS Full analysis set; GIC Global impression of change.

Data cut-off: 29 June 2018.

Source: Figure 11.2.3.7.2.3 and Figure 11.2.3.7.2.4, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

Figure 13 SPRINT Phase II Stratum 1: Correlation Between Change in NRS-11, in Patients with a Target Tumor Pain Intensity Score of 2 or More at Baseline, and Percent Change in Target PN Volume from Baseline to Pre-Cycles 5, 9, 13 and 25 (FAS)



Patients aged 8 to 18 years at enrolment were expected to complete self-report measures of the NRS-11.

Note: Only patients with a pain score ≥ 2 at baseline were included.

Pre-Cycle 5 Spearman rank correlation coefficient = 0.07.

Pre-Cycle 9 Spearman rank correlation coefficient = 0.76.

Pre-Cycle 13 Spearman rank correlation coefficient = 0.13.

Pre-Cycle 25 Spearman rank correlation coefficient = 0.71.

CSR Clinical study report; FAS Full analysis set; NRS-11 Numerical Rating Scale-11; PN Plexiform neurofibroma.

Source: Figure 11.2.3.2.7.2.2.1, SPRINT Phase II Stratum I CSR, Module 5.3.5.2.

The Applicant's Position:

PRO Compliance

Overall, compliance was high for all PROs, based on the number of patients/parents expected to complete each PRO, supporting the validity of any conclusions drawn.

Pain

The effect of selumetinib on pain was assessed through (1) self-evaluation of pain intensity (NRS-11) of the tumor (target PN) PN selected by the physician, of the tumor selected by the patient, overall tumor pain and the other pain and (2) how pain interferes with daily functioning (PII), which was rated by the patient and by the parent. In addition, patients recorded the pain medication that was used in the 1 week prior to enrolment in a pain medication survey. During

study treatment, pain medication/analgesia was recorded within concomitant medications, regardless of indication for its use. Pain palliation was based on 2 related components (1) reduction in pain intensity based on NRS-11 physician-selected tumor pain score and (2) stability or reduction in analgesic use, represented by no increase or reduction in analgesia use based on the World Health Organization Analgesia Ladder.

Reduction in pain intensity for self-selected and target tumor pain, overall tumor pain and other pain was seen as early as pre-Cycle 3 and maintained through pre-Cycle 25 (Figure 10).

There was a decrease from baseline in pain scores at each measurement cycle based on MMRM analysis (Table 33 and Figure 11). For the 24 patients with physician-selected target tumor scores who completed both baseline and pre-Cycle 13 assessments, the adjusted mean change from baseline was -2.07 (95% CI: -2.84, -1.31); 12/24 (50.0%) patients showed improvement of ≥ 2 points (CMT).); half of patients (12 of 24, 50.0%) showed a clinically meaningful reduction (improvement) in pain at pre-Cycle 13 (i.e., ≥ 2 -point decrease from baseline). Of the remaining 12 patients (50.0%) who experienced no change, 10 patients had a pain score of 0 or 1 at baseline and therefore had no possibility to improve their pain score by 2 points or more. No patients showed deterioration at pre-Cycle 13.

For patients with an NRS-11 score ≥ 2 at baseline (i.e., they had the possibility to improve by 2 points or more; n=14), pain palliation occurred early, within 2 to 4 months of treatment, and was sustained over time. The median time to pain palliation was reached by pre-Cycle 3 (1.9 months using the Kaplan Meier technique). This contrasts with published data from the Natural History study (Gross et al 2018), which showed that in the absence of surgical resection no symptomatic patients had improvement of their co-morbidities.

A decrease of 2 points on the NRS-11 was considered the CMT for this study population as this was reported in several studies in other populations and was also supported by the CMTs evaluated based on the distribution-based approach.

The improvements in pain are supported by self- and parent-reported changes in PII. There was a decrease from baseline in pain interference at each measurement cycle based on MMRM analysis (all p-values were $p < 0.05$). Of the 29 patients who completed both baseline and pre-Cycle 13 assessments, 10 (34.5%) patients showed improvement of ≥ 0.75 (CMT). Of the 18 (62.1%) patients who showed no change, 15 patients had a baseline score < 0.75 and therefore could not improve by the clinical meaningful threshold of 0.75 or more. One (3.4%) patient showed deterioration at pre-Cycle 13. Similar results were observed on parent-reported pain interference.

The improvements in pain are further supported by self- and parent-reported changes in tumor pain and overall pain as assessed by the GIC instrument (Figure 12). The proportion of parents who reported improvements (very much/much improved) in their child's tumor pain increased consistently from baseline (34.5% and 17.2%, respectively at pre-Cycle 13). Worsening of tumor pain and overall pain was seldom reported by patients or parents (only 1 patient at pre-Cycle 13 reported minimally worse pain; none reported much or very much worse).

Motor

The effect on motor function was evaluated in the strength of muscle groups and ROM of joints that were allocated in the same quadrant as the target PN. There were 33 patients with motor morbidity at enrollment; of these, 12 patients had their target PN at the unilateral lower quadrant, 1 patient at the bilateral lower quadrant, 11 patients at the unilateral upper and 7 patients at the bilateral upper quadrant. A sub-group analysis was performed based on PN body quadrant (upper and lower body quadrant) to allow for a more meaningful comparison to baseline.

There was a trend for improvement in strength and ROM (regardless of the location of the target PN) based on MMRM analyses.

In the subgroup of patients who had their target PN located in a unilateral upper body quadrant:

- Strength at pre-Cycle 13 (n=11): 1 (9.1%) patient showed improvement in strength of ≥ 0.43 (CMT). Of the 10 (90.9%) patients who showed no change, 7 patients had a strength MMT score >4.57 at baseline and therefore could not improve by the CMT of 0.43. No patient showed deterioration in strength at pre-Cycle 13.
- ROM at pre-Cycle 13 (n=9): 4 (44.4%) patients showed improvement in ROM of ≥ 112.25 degrees (CMT) and 5 (55.6%) patients showed no change. No patient showed deterioration in ROM at pre-Cycle 13.

In the subgroup of patients who had their target PN located in a unilateral lower body quadrant:

- Strength at pre-Cycle 13 (n=10): 5 (50.0%) patients showed improvement and 5 (50.0%) patients showed no change at pre-Cycle 13; of these, 3 patients had a strength MMT score >4.73 at baseline and therefore could not improve by 0.27 (CMT). No patient showed deterioration at pre-Cycle 13.
- ROM at pre-Cycle 13 (n=10): 1 (10.0%) patient showed improvement of ≥ 33 degrees (CMT), 8 (80.0%) patients showed no change and 1 (10.0%) patient showed deterioration at pre-Cycle 13.

For PROMIS, there was a trend towards improvement in mobility (as rated by parents) at each time point and a trend towards improvement in upper extremity physical function at pre-Cycle 25. Some patients showed clinically meaningful improvement on self-reported

mobility total scores (6 of 20 patients, 30.0%) and upper extremity scores (5 of 19 patients, 26.3%), with only few patients showing deterioration from baseline to pre-Cycle 13 for the self-reported mobility and upper extremity scores (2 patients each). Several patients had a score that was too high at baseline and therefore could not improve by the required CMT. A similar trend was observed for parent-reported scores, where some patients showing clinically meaningful improvement on mobility total scores (9 of 28 patients, 32.1%) and upper extremity scores (4 of 27 patients, 14.8%); no patients and 2 patients showing deterioration from baseline to pre-Cycle 13 for the parent-reported mobility and upper extremity scores, respectively. Several patients had a score that was too high at baseline and therefore could not improve by the required CMT.

PedsQL

Patient reported (≥ 8 years of age) and parent reported (all patients) HRQoL was assessed using the PedsQL questionnaire. There was improvement in self- and parent-reported HRQoL over time based on mean change from baseline in PedsQL total score and domain scores. Based on MMRM analysis of PedsQL total score, patients and parents reported improvement in HRQoL for patients at pre-Cycle 13 which was maintained through pre-Cycle 25. There was an increase from baseline in PedsQL total scores at each measurement cycle, which indicates improved HRQoL. Based on self-reported PedsQL total scores, at pre-Cycle 13 (n=29), 11 (37.9%) patients showed improvement based on a CMT of ≥ 10.33 . Based on parent-reported PedsQL total scores, at pre-Cycle 13 (n=45), 24 (53.3%) patients showed improvement based on a CMT of 11.90.

Airway

In SPRINT Phase II Stratum 1, 16 patients had airway dysfunction at baseline. The majority of these (14 of 16 patients) had 3 (7 patients) or 4 (7 patients) baseline PN-related morbidities assigned to their target PN, showing the complexity and burden of symptoms in these patients. Five of these patients required airway support at baseline (such as tracheostomy), which limited their ability to perform pulmonary functioning tests. Of note, 1 patient was able to be decannulated and was still in response at pre-Cycle 25 and was still receiving selumetinib at study DCO.

A percentage change of $\geq 12\%$ in FEV1 (litres) was classified as an improvement, as recommended by the REiNS functional group (Plotkin et al 2016). FEV1 showed a positive trend from baseline (i.e., improvement) to pre-Cycle 13. At pre-Cycle 13, most patients (63.6%) showed improvement, with no patients showing deterioration in FEV1.

AHI is the number of apnoeas or hypopnoeas recorded per hour of sleep. At baseline, no patient had an AHI of >5 events per hour; therefore, no patient met the REiNS criteria (>5 events/hour) for inclusion in sleep studies as they would be unable to improve enough to meet criteria for functional improvement.

The mean baseline AHI was 1.407 events per hour (n=14). For the 13 patients who had both baseline and pre-Cycle 13 sleep assessments, 6 patients had an AHI >1 event per hour at baseline (AHI >1 event per hour indicates sleep disturbance) and, of these, none had an increase in AHI at pre-Cycle 13.

Patients with airway PN did not demonstrate an overall mean change from baseline in the 6MWT at pre-Cycle 13, however, 12 of the 16 patients with airway dysfunction also had motor dysfunction which may have affected the test.

Orbit

Relatively few patients (n=10) were assigned a visual (orbit) PN-related morbidity, and for half (5 of 10) of the patients, there was no possibility of improvement in visual acuity from baseline, since the affected eye had either been enucleated (2 patients), vision was limited to light perception and position (1 patient) or patients had no light perception (2 patients).

Bowel/Bladder

For bowel and bladder functioning, relatively few patients (n=10) were assigned a bowel and bladder functioning PN-related morbidity, with insufficient baseline data to evaluate mean change for self-report scores and only a trend of improvement for parent-reported scores in the DVQ questionnaire.

For patients assigned a visual morbidity, or for patients assigned a bowel and bladder functioning morbidity, it is challenging to try and draw conclusion at a population level, and the IPRs (see Section 8.1.1) are more informative to understand changes in these morbidities in the context of other assigned morbidities and changes in target PN volume.

Correlation Analyses

The Spearman rank correlation coefficients (r), which measure strength of rank preserving relationship, were assessed per Cohen (1988). Whilst a weak correlation coefficient indicates a lack of evidence of a rank preserving relationship, it should not be interpreted as lack of relationship in general (r=0 to 0.3 equates to a weak correlation, r=0.3 to 0.5 equates to a moderate correlation, r=0.5 to 1.0 equates to a strong correlation.)

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

Pain

To assess the correlation between change in NRS-11 and percent change in target PN volume from baseline to pre-Cycles 5, 9, 13, and 25, patients with a score of ≥ 2 at baseline were analysed (Figure 13).

- At pre-Cycle 5, the majority of patients have shown reduction in tumor volume as well as reduction in NRS-11 score. However, the scatter plot is compact, with the deepest shrinkage at -20% and the strongest pain improvement at -4 (except for 1 patient). Weak correlation (r of 0.07) was observed at this point.
- At pre-Cycle 9, all but 2 patients have shown reduction in tumor volume, of whom all have shown reduction in NRS-11 score. The scatter plot expands as PN shrink more and even stronger pain improvement is observed (more patients beyond -4). A strong correlation can be observed at this point, with a correlation coefficient of 0.76.
- At pre-Cycle 13, the same pattern is observed with the exception of 2 outliers which neutralize the correlation coefficient (0.13, weak correlation).
- At pre-Cycle 25, the pattern is similar to pre-Cycle 9 and pre-Cycle 13 but without the 2 outliers, resulting in a strong correlation (r of 0.71).

Longitudinal analyses were also performed for NRS-11. After adjusting for age, number of morbidities and the baseline value of the clinical outcome, there was evidence of a meaningful correlation between percentage change from baseline in target PN volume and change in NRS-11 score ($p < 0.001$). This analysis demonstrates that improvement in pain intensity strongly correlates with reduction in PN volume.

Motor

Despite potential confounding factors affecting motor function (including the anatomical location of the PN, and the degree of other associated symptoms including pain at baseline); several correlations between percentage change in PN volume and motor function were observed.

In terms of strength, a weak correlation was observed between change from baseline to pre-Cycle 13 in strength MMT and percent change in target PN volume (r was 0.06). A correlation was observed between the change from baseline to pre-Cycle 13 in ROM and percent change in target PN volume (r was -0.24) indicating gain in ROM as the PN shrinks.

The Spearman rank coefficients (r) for the change from baseline for the PROMIS self-reported and parent-reported scores (mobility) and percent change in target PN volume at pre-Cycle 13 are 0.11 (weak correlation) and -0.43 (moderate positive correlation), respectively. The r for the correlations with change from baseline for the PROMIS self-reported and parent-reported scores (upper extremity) and change in target PN volume at pre-Cycle 13 are -0.30 (moderate positive correlation) and -0.16 (weak positive correlation), respectively. These correlations suggest that increasing PROMIS transformed scores, which indicate better physical functioning, were associated with decreasing target PN volumes.

Correlations with percentage change in target PN volume were also detected in the longitudinal models of change in parent-reported PROMIS scores (both mobility $p=0.042$ and upper extremity $p=0.034$).

PedsQL

A clear positive correlation was observed between percentage change in PN volume and parent-reported PedsQL total scores; with a similar observation for the physical, emotional and social functioning subscales. These results indicate that HRQoL improvement is associated with decreasing target PN volume. This correlation was also detected in the longitudinal mixed model of change in parent-reported PedsQL total score ($p=0.033$).

The correlation with self-report PedsQL total score is less apparent as it was impacted by 2 patients who were considered outliers (patients with a PN growth $>10\%$ who reported substantial improvement in HRQoL).

Airway

The Spearman rank coefficients (r) was 0.39, which indicates a moderate positive correlation between the change from baseline to pre-Cycle 13 in AHI and percent change in target PN volume. However, the baseline AHI was below the REiNS criteria (≤ 5 events/hour) for inclusion in sleep studies and, thus, the results should be interpreted with caution.

The FDA's Assessment:

The FDA does not agree with the analyses and interpretation of the results presented by the applicant in this section for physician selected target PN pain intensity, pain interference, and health related quality of life. The trial collected a number of PROs, observer-reported outcomes (ObsROs) and performance observations (PerfO). The FDA analysis focused on pain NRS, pain interference and HRQL. Pain NRS was captured using 4 items that asked patients to select one number from 0 to 10 that best described their worst pain over the past week for the following: 1) overall pain, 2) overall tumor pain, 3) pain for a specific tumor patients choose, and 4) pain for a specific tumor physicians choose. The Pain Interference Index, which is 6-item measure that assesses the degree to which pain interfered with daily activities in the past week. And the PedsQL, a 23-item measure of global QOL with 4 subscales: physical functioning, emotional functioning, social functioning, and school functioning. For children aged 2 – 18 the parent-reported version was administered and for children 8 – 18 the self-report versions were administered. The completion rates for these instruments were high and are presented in FDA Table 34. However, all of these analyses are exploratory and there are several challenges associated with the analysis and interpretation of this data. These include lack of a comparator arm, and by extension, parent/caregiver's knowledge of treatment assignment, a small sample size, potential instrument limitations, thresholds used for defining clinically meaningful change, and assumptions of the MMRM.

Table 34 Completion Rates of Selected PRO Endpoints

	Baseline n (%) ¹	Pre-cycle 3n (%)	Pre-cycle 5 n (%)	Pre-cycle 9 n (%)	Pre-cycle 13 n (%)	Pre-cycle 25 n (%)
<i>Pain Intensity by NRS-11 (patient-reported), n = 34</i>						
Eligible	26	25	25	24	24	19
Assessed	26 (100)	25 (96)	25 (96)	24 (92)	24 (92)	18 (73)
<i>Pain interference using PII completion rate (patient-reported), n = 34</i>						
Eligible	34	32	32	30	30	23
At least one question completed	33 (97)	31 (91)	31 (91)	29 (85)	29 (85)	23 (68)
All questions completed	32 (94)	30 (88)	30 (88)	27 (79)	28 (82)	23 (68)
<i>Pain interference using PII completion rate (parent/guardian-reported), n = 50</i>						
Eligible	48	46	46	43	43	34
At least one question completed	47 (98)	46 (96)	45 (94)	43 (90)	43 (90)	34 (71)
All questions completed	46 (96)	45 (94)	43 (90)	41 (85)	42 (88)	34 (71)
<i>HRQOL using PedsQL (patient-reported), n = 34</i>						
Eligible	34	32	32	30	30	23
At least one question completed	33 (97)	31 (91)	31 (91)	29 (85)	29 (85)	23 (68)
All questions completed	27 (79)	21 (62)	20 (59)	23 (68)	24 (71)	19 (56)
<i>HRQOL using PedsQL (parent/guardian-reported), n = 50</i>						
Eligible	50	48	48	45	45	35
At least one question completed	50 (100)	48 (96)	47 (94)	45 (90)	45 (90)	35 (70)

¹Percentages are reported as percent of baseline PRO-evaluable patients

There were challenges with regard to the analysis of the pain NRS, as the primary focus of the analysis was on the results from the NRS-11 physician-selected tumor pain score. Due to a change in the protocol, only 24 patients of the 34 patients eligible to respond (i.e., patients age > 8 years) completed this particular pain item. No deteriorations were reported at the pre-cycle 13 (i.e., approximately 1 year post baseline), and the majority of patients classified as stable had either no pain or pain that could not reduce by ≤ 2 points at baseline. As pain was measured infrequently, it is difficult to interpret the pain results, and this may help to explain

the weak correlation results with tumor shrinkage.

Results from the PII support the finding that pain did not appear to be getting worse while on treatment with only one patient reporting a deterioration on PII.

For PedsQL all items exhibit some degree of floor effects (i.e., more than 20% of patients responding to the lowest response option) indicating this tool may be limited in detecting change in HRQL and other domains. In addition, the total score of the PedsQL includes a number of items that are considered distal to the drug effect (e.g., “others tease me” or “it’s hard to pay attention in class”). In examining the physical function domain, mean change for physical functioning from the self-report PedsQL for participants 8 and older indicated that on average patients had improvements over the course of the treatment. The same pattern was observed for the parent-reported physical function score of the PedsQL.

The analyses of the other PRO and performance endpoints presented in this section are considered exploratory. FDA considered other endpoints presented in this section to be supportive but did not independently verify the results.

Additional Analyses Conducted on the Individual Trial

Data:

Table 35 SPRINT Phase II Stratum 1: Target PN Measurements Margin of Error: ICR Assessment

Variance Component and ICC	Estimate
Intra-subject (or inter-reader) standard deviation ¹	100.19
Inter-subject standard deviation ²	1277.24
ICC ³	0.99

¹ Describes the variability in measurements made in the same scans by the 2 different independent reviewers (in mL).

² Describes the variability in the 10 target PN baseline volumes between patients (in mL).

³ Defined as the ratio of the inter-subject variance to the sum of the inter-subject and intra-subject variances. An ICC value of 1 indicates that the margin of error for target PN measurements (intra-subject variability) is zero. The inter-subject and intra-subject standard deviations have been estimated from a mixed model with no fixed effects and a random effect for subjects.

CSR Clinical study report; ICC Intraclass correlation coefficient; ICR Independent central review; PN Plexiform neurofibroma.

Source: Table 11.2.2.4, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

Table 36 SPRINT Phase II Stratum 1: Repeated Target PN Measurements Margin of Error: ICR Assessment

Variance Component and ICC	Estimate
Intra-subject (or inter-reader) standard deviation ¹	5.75
Inter-subject standard deviation ²	16.82
ICC ³	0.90

¹ Describes the variability in measurements made in the same scans by the 2 different independent reviewers over time (in percent).

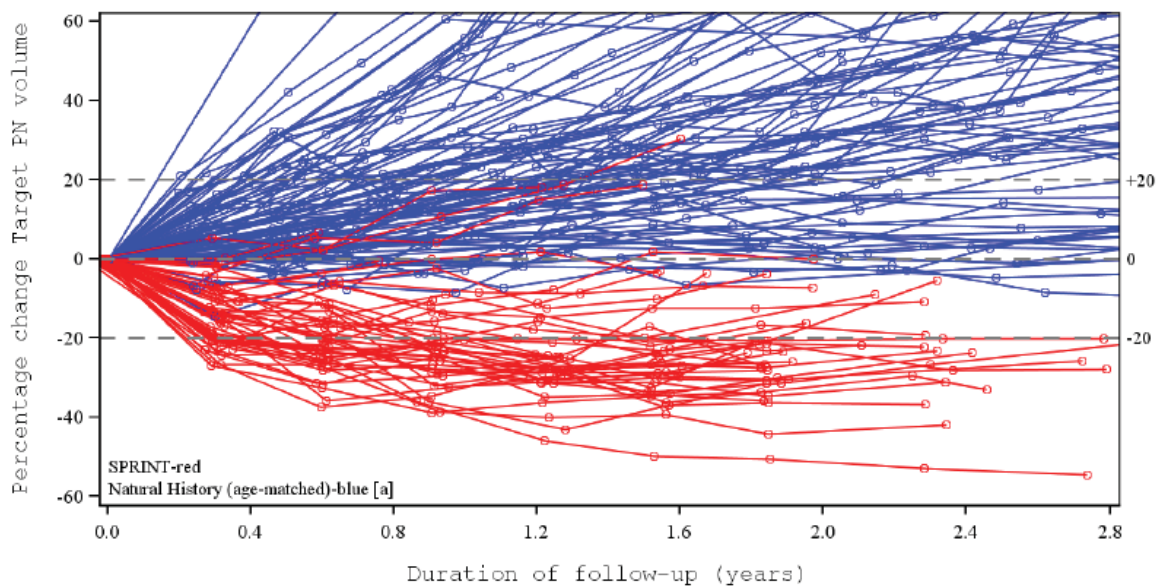
² Describes the variability in the percent change from baseline in 10 target PN volumes between patients (in percent).

³ Defined as the ratio of the inter-subject variance to the sum of the inter-subject and intra-subject variances. An ICC value of 1 indicates that the margin of error for target PN measurements (intra-subject variability) is zero. The inter-subject and intra-subject standard deviations have been estimated from a mixed model with percent change from baseline in target PN volume as the response, time as fixed effect, and reader, subject, reader-subject, reader-time and subject-time interactions as random effects.

CSR Clinical study report; ICC Intraclass correlation coefficient; ICR Independent central review; PN Plexiform neurofibroma.

Source: Table 11.2.2.4.1, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

Figure 14 Percentage Change in Target PN Volume, Natural History Study (Age-matched; External Control) and SPRINT Phase II Stratum 1 (Pivotal Data), Individual Patient Data Aligned to the Maximum Duration of SPRINT Phase II Stratum 1



^a Includes patients aged 3 to 18 years with at least 1 volumetric MRI within this age and 1 subsequent volumetric MRI.

Note: 92 patients are presented in this plot for Natural History and 48 patients for SPRINT Phase II Stratum 1.

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Patients with at least 2 volumetric MRI assessments in each study (including baseline for SPRINT Phase II Stratum 1) are displayed in this figure. Note that the figure includes the 2 patients with only 1 volumetric MRI scan within the 2.8 years although these patients are not included in the growth analysis aligned to 2.8 years.

Figure includes data up to maximum SPRINT Phase II Stratum 1 follow-up duration.

CSR Clinical study report; DCO Data cut-off; MRI Magnetic resonance imaging; PN Plexiform neurofibroma
DCO: 15 October 2018.

Source: Figure 11.2.7.6, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2

Table 37 Target PN Growth Rate in Patients Aged ≥3 to <18 years, Natural History Study (Age-matched) and SPRINT Phase II Stratum 1

Group	n	Time Period, Years ¹ Median (min, max)	PN Volume % Change/Year ² Median (min, max)	Estimated Annual PN Growth Rate Mixed Model ³	
				Adjusted Mean	95% CI
SPRINT Phase II Stratum 1 (pivotal data) ⁴	48	1.8 (0.3, 2.8)	-10.2 (-27.3, 19.0)	-16.9	-20.2, -13.5
Natural History study (age-matched and aligned to maximum FU duration of SPRINT Phase II Stratum 1) ^{5,6} (external control)	90	2.5 (0.8, 2.8)	21.3 (-4.1, 147.9)	21.3	15.9, 26.8
Natural History study (age-matched) (external control) ⁶	92	6.8 (1.0, 17.7)	15.1 (-3.7, 126.2)	20.5	16.5, 24.5

¹ Natural History: Time period was defined from the first to the last available volumetric MRI assessment or last volumetric MRI assessment date prior to the first use of a MEK inhibitor, including selumetinib. SPRINT Phase II Stratum 1: Time period was defined from the baseline volumetric MRI assessment date until the last evaluable assessment date up to data cut-off or treatment discontinuation (whichever occurred first).

² Percentage PN volume change from the first volumetric MRI assessment (baseline assessment for SPRINT Phase II Stratum 1) to the last volumetric MRI assessment over that time period in years.

³ Mixed models included percentage change in PN volume as response, time (in years), age at baseline and baseline PN volume as covariates. Natural History mixed models also contained a quadratic term for time.

⁴ Included patients with baseline and at least 1 subsequent volumetric MRI assessment.

⁵ Includes data up to maximum SPRINT Phase II Stratum 1 follow up duration.

⁶ Includes patients aged 3 to 18 years with at least 1 volumetric MRI within this age and 1 subsequent volumetric MRI.

CI Confidence interval; CSR Clinical study report; FU Follow-up; Max Maximum; MEK Mitogen-activated protein kinase kinase; Min Minimum; MRI Magnetic resonance imaging; NCI National Cancer Institute; NF1 Neurofibromatosis type 1; PN Plexiform neurofibroma.

Data cut-off: 15 October 2018

Source: Table 11.2.4.3, SPRINT Phase II Stratum 1 CSR, Module 5.3.5.2.

The Applicant's Position:

Margin of Error for Target PN Measurements Estimated by Inter-reader Variability

Following FDA request, the margin of error for target PN measurements at baseline and over time was also assessed.

The margin of error for target PN measurements at baseline between the 2 readers was assessed using the ICC, which indicated excellent agreement (ICC of 0.99; Table 35). The inter-reader SD (100.19 mL) is more than 12 times smaller than the inter-subject SD (1277.24 mL); this indicates a very small margin of error in estimating target PN volume at baseline.

The margin of error for percentage change in target PN volume between the 2 readers across timepoints was assessed using the ICC, which indicated excellent agreement (ICC of 0.90; Table 36). The inter-reader SD (5.75%) is approximately 3 times smaller than the inter-subject SD (16.82%); it indicates a relatively small margin error in estimating percentage change in PN volume. Therefore, the threshold to determine PR (a PN decrease $\geq 20\%$ compared with baseline) is clearly outside of the margin of error for PN measurements.

Volumetric PN Growth in SPRINT Phase II Stratum 1 and the NCI POB NF1 Natural History Study (Age-matched)

The Natural History age-matched cohort (N=92) comprised patients aged 3 to 18 years at the time of enrollment who had at least 1 volumetric MRI within this age and at least 1 subsequent volumetric MRI.

Spaghetti plots showing individual patient PN volumes over 2.8 years and change in target PN volume over time are presented in Figure 14 (y-axis range: -60% to +60%) for SPRINT Phase II Stratum 1 and the Natural History Study age-matched cohort.

The plot shows that patients treated with selumetinib in SPRINT Phase II Stratum 1 demonstrated durable and sustained PN responses ($\geq 20\%$ reduction in target PN volume from baseline) or PN volume stabilisation ($< 20\%$ change in PN volume from baseline). In the Natural History age-matched cohort the vast majority of PN grew continuously over time or at best remained stable in size ($< 20\%$ change in PN volume from baseline). There was no spontaneous PN shrinkage of $\geq 20\%$ within 1 year in the Natural History study.

Over a 2.8-year period, the median PN volume change per year in SPRINT Phase II Stratum 1 was -10.2% (range -27.3% to +19.0%), whereas in the Natural History age-matched cohort it was +21.3% (range -4.1% to +147.9%). The adjusted mean annual PN growth rate was -16.9% (95% CI: -20.2, -13.5) per year in SPRINT Phase II Stratum 1, versus +21.3% (95% CI: +15.9, +26.8) in the Natural History age-matched cohort (Table 37).

The natural course of a PN is to grow over time and, as shown in this Natural History age-matched cohort, at least half of these children have an annual growth of their PN by over

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+21%. Spontaneous PN shrinkage has been documented for few patients at -4% per year. In comparison, the median tumor reduction was -10% per year in SPRINT Phase II Stratum 1, indicating that this degree of shrinkage can be attributed to selumetinib treatment, rather than to natural course of the disease.

The FDA's Assessment:

The analyses presented in this section are exploratory and were not verified by the FDA.

8.1.3. SPRINT Phase I

Trial Design

The Applicant's Description:

This was a CTEP-sponsored Phase I, open-label, single-arm, multiple dose, dose-escalation, multi-centre study of selumetinib in pediatric patients with NF1 and inoperable PN, and was conducted by the NCI POB. At least 21 patients aged ≥ 3 and ≤ 18 years, with the ability to swallow whole capsules (as capsules cannot be crushed or broken), were planned for enrolment. Selumetinib was administered orally BID (approximately every 12 hours) on a continuous schedule; the dose was capped at 50 mg when BSA was ≥ 1.9 m². A cycle of treatment was 28 days with no rest periods between cycles.

The schedules for volumetric MRI assessments was pre-study; prior to Cycles 6 and 11, and every 6 cycles thereafter.

The same volumetric MRI method and analysis was used to measure target PN size and change in volume in SPRINT Phase I and Phase II Stratum 1, including review of volumetric MRIs by the same NCI POB central reviewer.

Efficacy endpoints evaluated in Phase I include ORR, DoR and TTR (all exploratory).

The FDA's Assessment:

The FDA agrees to the Applicant's description of the trial design.

8.1.4. **SPRINT Phase I Study Results**

Compliance with Good Clinical Practices

The Applicant's Position:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements and relevant CTEP and study centre guidelines.

The FDA's Assessment:

See the FDA Assessment in Section 8.1.2.

Financial Disclosure

The Applicant's Position:

See Section 19.2.

The FDA's Assessment:

See the FDA Assessment in Section 8.1.2. and 19.2.

Patient Disposition

Data:

See the Applicant's Position below.

The Applicant's Position:

In SPRINT Phase I, at DCO in SPRINT Phase I (29 June 2018), 13 (54.2%) patients remained on selumetinib treatment; 3 (12.5%) patients had discontinued selumetinib but remained on-study. In total, 11 patients discontinued selumetinib; the reasons were: AE (3 patients), disease progression (2 patients), patient not willing to continue (2 patients), treatment period completed (1 patient) and other (3 patients). Three patients discontinued and re-started selumetinib during the study; 2 of these patients remained on selumetinib at DCO and 1 patient discontinued a second time. Eight patients terminated the study; the reasons were voluntary discontinuation by patient (4 patients), disease progression (2 patients), AE (1 patient) and other (1 patient). There were no deaths during SPRINT Phase I.

The FDA's Assessment:

The FDA agrees with the results for the patient disposition of SPRINT Phase I presented in this section

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Protocol Violations/Deviations

Data:

See the Applicant's Position below.

The Applicant's Position:

In SPRINT Phase I, 2 (8.3%) patients had important protocol deviations; both were dosing schedule modifications and neither of the important deviations influenced the overall efficacy conclusions.

The FDA's Assessment:

See the FDA Assessment in Section 8.1.2.

Table of Demographic Characteristics

Data:

Table 38 SPRINT Phase I: Patient Disposition (All Patients)

		Total¹ (N=24)
Age, years ²	n	24
	Mean (SD)	10.89 (4.684)
	Median (min, max)	10.90 (3.0-18.5)
Sex, n (%)	Male	13 (54.2)
	Female	11 (45.8)
Race, n (%)	White	18 (75.0)
	Asian	2 (8.3)
	Black or African American	2 (8.3)
	Unknown	2 (8.3)
Ethnic group, n (%)	Not Hispanic or Latino	21 (87.5)
	Hispanic or Latino	2 (8.3)
	Unknown	1 (4.2)
Height, cm	n	24
	Mean (SD)	136.313 (24.1577)
	Median (min, max)	135.600 (98.50-173.63)
Weight, kg	n	24
	Mean (SD)	37.85 (19.958)
	Median (min, max)	30.34 (16.8-88.7)
BSA, m ²	n	24
	Mean (SD)	1.180 (0.4053)
	Median (min, max)	1.070 (0.67-2.01)

¹ Includes 12 patients who received selumetinib 20 mg/m² BID, 6 patients who received selumetinib 25 mg/m² BID and 6 patients who received selumetinib 30 mg/m² BID.

² Age was calculated using the date of informed consent.

BID Twice daily; BSA Body surface area; Max Maximum; Min Minimum; SD Standard deviation.

Source: Table 11.1.4 and Table 11.1.5.

The Applicant's Position:

In SPRINT Phase I, the majority of patients were White and the median age was 10.9 years (range: 3.0 to 18.5 years; see Table 38).

The FDA's Assessment:

The FDA agrees with the results presented in this section.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

See the Applicant's Position below.

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The Applicant's Position:

In SPRINT Phase I, the median time from diagnosis of PN to start of selumetinib treatment was 8.28 years (range: 0.79 to 17.00 years). The target PN volume at baseline ranged from 29.4 to 8744.0 mL and the median target PN volume was 1204.50 mL and most patients had minor restrictions in physically strenuous activity at baseline. Target PN were located in different body sites for different patients and 1 patient had a whole body PN.

The FDA's Assessment:

The FDA agrees with the results presented in this section

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance

Data:

Treatment adherence for Cycles 1 to 3 is summarized in Table 11.3.1.3, SPRINT Phase I CSR, Module 5.3.5.2).

The Applicant's Position:

Treatment adherence was high.

Concomitant medications

Data:

The most common concomitant medications (>40% of patients) were ondansetron (58.3%), clindamycin (54.2%; topical use in most cases), ibuprofen (54.2%), hydrocortisone (50.0%; topical use), amoxicillin (50.0%), cephalexin (45.8%), and paracetamol (45.8%).

The Applicant's Position:

Use of concomitant treatments during the study were not considered to have impacted the study results.

The FDA's Assessment:

The results of SPRINT Phase I were considered exploratory, and an in depth analysis of concomitant medications was not verified by the FDA.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Not applicable (SPRINT Phase I had no primary efficacy endpoints).

The Applicant's Position:

Not applicable (SPRINT Phase I had no primary efficacy endpoints).

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The FDA's Assessment:
Not Applicable.

Data Quality and Integrity

Data:

SPRINT Phase I was conducted at pediatric hospitals leading in care of patients with NF1-related PN. Phase I was monitored by CTEP via quarterly data submissions in Clinical Data Update System. On-site audits were to be conducted at all participating sites by the [REDACTED] (b) (4) [REDACTED] conducted 1 tri-annual audit in May 2014 and monitored 11 patients.

The C3D was used to collect safety and efficacy data from SPRINT Phase I.

The Applicant's Position:

Study conduct, quality and integrity were appropriate for this study.

The FDA's Assessment:

The FDA acknowledges the Applicant's description of CTEP trial monitoring procedures, data collection methods, and the independent audits that were conducted for the phase 1 portion of SPRINT. See Section 8.1.2 *Data Quality and Integrity* for the FDA's assessment of overall data quality and integrity in the NDA.

Efficacy Results – Secondary and other relevant endpoints

Data:

See the Applicant's Position below.

The Applicant's Position:

ORR

The ORR observed in SPRINT Phase I study was 66.7% [16 of 24 patients] 95% CI 44.7%, 84.8%.

Supplementary analyses were performed to derive ORR based on all available volumetric MRI scans. For SPRINT Phase I, one more confirmed PR was observed when including all available volumetric MRI scans (17/24 patients [70.8%]).

PFS

In SPRINT Phase I, only 2 patients progressed hence the median PFS was not reached.

A supplementary analysis was performed to derive PFS based on all available volumetric MRI scans. According to this analysis, in SPRINT Phase I, 4/24 (16.7%) patients progressed, i.e., 2 more patients than were found to have progressed in the main PFS analysis.

TTP

No deaths were observed SPRINT Phase I, hence TTP results are the same as of PFS presented above.

TTR

In SPRINT Phase I, 81.3% of the patients with confirmed objective response had target PN shrinkage of $\geq 20\%$ from baseline within 10 cycles. Since there were 5 cycles between the first and second volumetric MRI scans, the median time to onset of response was 7.5 cycles.

The FDA's Assessment:

The FDA agrees with the results for the overall response rate from the SPRINT Phase I study presented in this section; however, this data is considered descriptive only.

Additionally, the FDA considers time-to-event endpoints uninterpretable in a single-arm trial. These analyses are considered exploratory and were not verified by the FDA.

Dose/Dose Response

Data:

The PK exposure from the doses evaluated in SPRINT Phase I indicated a dose proportional increase; however, as the difference in dose was approximately 20% between doses, the exposures were overlapping across these doses. The dose-efficacy relationship from SPRINT Phase I indicated that ORR was broadly similar across doses.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

See FDA assessment under Section 6.2.2.1.

Data:

See Applicant's Position below.

The Applicant's Position:

At the DCO for SPRINT Phase I, all patients with a confirmed response had been followed up for at least 16 months from the onset of response; follow-up time from the onset of responses ranged from 18 to 65 cycles. Similar to SPRINT Phase II Stratum 1, median DoR from onset of response was not reached as only 1 of the 16 confirmed responders (i.e., cPR) had subsequently progressed by the study DCO. All 16 patients who were confirmed responders were still in

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response after 16 cycles from the onset of response. The estimated proportion of patients remaining in response after 52 cycles, estimated using the Kaplan-Meier method, was 100%.

Supplementary analyses were performed to derive DoR based on all available volumetric MRI scans confirmed the responses to be highly durable with the probability of still being in response 46 months after onset of response was 90.0% (95% CI: 47.3, 98.5). Median DoR was not reached (95% CI:41.8, not calculated)

The FDA's Assessment:

Given the small sample of patients with a confirmed response, this analysis is considered exploratory. The FDA calculation of estimates of duration of response considered time as measured by dates rather than treatment cycle. Per the FDA calculation, the median DOR was not reached, all 16 responders remained in response for more than 12 months from the onset of response, and the duration of response ranges from 16.4 to 63.3 months. The FDA did not verify the supplementary analyses results presented in this section.

Persistence of Effect

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment: Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment: Not applicable.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

See Section 8.1.7.

8.1.6. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

See the Applicant's Position below.

The Applicant's Position:

Objective Response

Selumetinib demonstrated a confirmed ORR by NCI POB central analysis of 66.0% (95% CI: 51.2, 78.8), based on 33 responders from 50 evaluable patients in SPRINT Phase II Stratum 1. A further 4 (8.0%) patients had an unconfirmed partial response (PR). No patients had progression as their best response. Reduction in target PN volume was observed early, with almost all patients having a reduction in target PN volume by 4 cycles (i.e., pre-Cycle 5, median percentage change in target PN volume from baseline was -14.31% at this time point). Natural History study data indicate that the PN shrinkage observed in SPRINT Phase II Stratum 1 can be attributed to selumetinib, rather than the natural course of the disease. The adjusted mean annual growth rate was +21.3% (95% CI: 15.9, 26.8) per year in the Natural History study age-matched cohort compared with -16.9% (95% CI: 20.2, -13.5) per year in SPRINT Phase II Stratum 1. Supportive ORR data from SPRINT Phase I (66.7% [16 of 24 patients]) confirmed the high ORR observed in SPRINT Phase II Stratum 1.

The FDA's Assessment:

The FDA agrees with the response results for SPRINT Phase II Stratum 1; however, considers any comparison of results between the SPRINT Phase II Stratum 1 and the Natural History study as exploratory due to the lack of information available to adjust any comparison for potential confounding or bias.

Secondary and Other Endpoints

Data:

See the Applicant's Position below.

The Applicant's Position:

Duration of Response

The median DoR from onset of response based on NCI POB central analysis was not reached in either the pivotal SPRINT Phase II Stratum 1 or supportive Phase I data. Of the 33 responders in SPRINT Phase II Stratum 1 and the 16 responders in SPRINT Phase I, the probability of remaining in response, after 12 cycles and 52 cycles, respectively, estimated using the Kaplan-Meier method, was 100%.

Progression-free Survival

Very few patients progressed in either SPRINT Phase II Stratum 1 (3 patients) or SPRINT Phase I (2 patients). Median PFS was not reached in either trial. The PFS benefit of selumetinib treatment observed in SPRINT Phase II Stratum 1 was confirmed by the Natural History age-matched cohort as most patients in this cohort had progressed (76.1%), median PFS was 1.3 years (95% CI: 1.1, 1.6) with the probability of remaining without progressive disease after 2 years of 30.4% (95% CI: 21.0, 40.3). In addition, the PFS benefit of selumetinib treatment in observed in SPRINT Phase II Stratum 1 was also confirmed by the placebo arm of tipifarnib Study 01-C-0222, (patients with progressive PN) where most patients in this control group had progressed (23 of 29 patients, 79.3%), median PFS was estimated as 1.0 year, with the probability of remaining without progressive disease after 2 years of 20.6% (95% CI: 7.7, 37.8).

The FDA's Assessment:

The FDA agrees with the results for DOR in SPRINT Phase II Stratum 1 presented in this section, but considers other results not interpretable.

Subpopulations

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

See Additional Efficacy Considerations

Additional Efficacy Considerations

The FDA's Assessment:

SPRINT Phase II Stratum 1 subgroup analyses

The FDA conducted additional analyses of ORR as assessed by the ICR for age, PN status, and PN classification at enrollment. The ORR (95% CI) in patients age >12 years was 29% (10%, 56%), and in patients age ≤ 12 years, the ORR was 52% (34%, 69%). The ORR (95% CI) in patients with progressive disease at enrollment was 57% (34%, 78%), whereas the ORR was 40% (16%, 68%) in patients with non-progressive disease.

Supportive ORR and DOR data

ORR and DOR was assessed for the 24 patients with NF1 PN enrolled in SPRINT Phase 1 and for the 25 patients enrolled in SPRINT Phase II Stratum 2. The NCI central review of ORR for these cohorts was 67% (16/24) (95% CI: 45, 84) and 68% (17/25) (95% CI: 47, 85) respectively. All of

the 16 responders (100%) in SPRINT Phase 1 and 12 of the 17 responders (71%) in SPRINT Phase II Stratum 2 had a duration of response $\geq$ 12 months from the onset of response.

Descriptive analyses of clinical outcomes data

The FDA additionally reviewed clinical outcomes data for the 33 patients in SPRINT Phase II Stratum 1 who had an objective response per NCI review using REiNS criteria. These data were considered part of the overall benefit assessment for selumetinib in NF1 PN.

NF1 PN is a tumor that presents in various locations, and tumor-related morbidity varies across patients as it is dependent in part on compression of surrounding normal structures. The SPRINT protocol therefore included multiple COA tools for supportive efficacy assessments due to the diverse tumor geography (e.g., PFTs and sleep studies for tumors near the airway, vision testing for orbital tumors, ROM and strength testing for extremity tumors, etc.). Given the rarity of this condition and the heterogeneity with regard to PN-related morbidity, the sample sizes for each morbidity category were small. These were exploratory endpoints intended to better characterize the clinical benefit of selumetinib in NF1 PN.

SPRINT Investigators assigned specific target PN-related morbidities to each patient at enrollment, and the clinical outcome measure related to the assigned morbidity was evaluated routinely with radiographic tumor volume assessments. The objective was to show that a reduction in tumor volume was reliably accompanied by a detectable effect on physical function or PN-related symptoms indicating that the patient's quality of life was improved. Given the benign nature of the tumor, this correlation was considered important in the overall benefit:risk assessment for selumetinib.

The Applicant submitted an IPR document (see Section 8.1.1, Additional Analyses) for each patient enrolled in SPRINT Phase II Stratum 1. The template content for the IPRs was agreed upon at the preNDA meeting. Table 39 summarizes the FDA review of tumor volume reduction in the context of supportive clinical outcomes data and important safety information for patients who experienced an objective response.

Table 39 SPRINT Phase II Stratum 1: Response, DoR, and Clinical Outcomes

Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
(b) (6)	16.7	5 surgeries 5 systemic	Head/orbit 356 mL	Vision Disfigurement	-23%, Cycle 21	22+	Baseline exophthalmos 24mm reduced to 14mm by Cycle 5 and remained WNL at Cycle 37.	No SAEs; Grade 3 CPK increase; no dose reduction	Patient self-reported ability to open eye more. Continued selumetinib at DCO. Inv. stated benefit.
	8.3	1 systemic	Neck/ext 1748 mL	Pain Motor Disfigurement	-34%, Cycle 21	30+	NRS-11 score 3 at baseline improved to 0 at cycle 5 and maintained. ROM increased. Small increases in strength.	No SAEs. Grade 3 pyrexia, weight gain, tumor pain; no dose reductions.	Tumor pain improved. Patient reported improved movement. Continued selumetinib at DCO. Inv. stated benefit.
	8.8	1 systemic	Neck 224 mL	Disfigurement	-31% Cycle 25	25+	Photos only	No SAEs; no Grade 3-4 AEs; no dose reductions.	Self and parent reported improvements in tumor size. Decrease in hyperpigmentation of skin over tumor noted. Continued selumetinib at DCO. Inv. stated benefit.
	5	3 systemic	Head/neck/ orbit 478 mL	Airway Vision Disfigurement	-33%, Cycle 21	29+	FEV1 75% of predicted at baseline. Increased to WNL cycle 5 and maintained. R20 airway impedance	No SAEs; no Grade 3-4 AEs; no dose reductions.	FEV1 improved from abnormally low for age at baseline and remained normal. VA results inconsistent with reports. Inv stated benefit and

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
							Improved. Sleep disturbance unchanged. VA decreased in both eyes. Parents reported improved vision.		patient continued selumetinib at DCO.
(b) (6)	6	3 surgeries 1 systemic	Head 295 mL	Vision Pain Disfigurement	-44% Cycle 25	24+	Decrease in PI and improved GIC by parent report. No change in VA.	No SAEs. Grade 3 lab changes; no dose reductions.	Parent reports eye opens better, less drooling, able to move lips and drink from a straw. Continued selumetinib at DCO. Inv. stated benefit.
	10	1 systemic	Neck 185 mL	Airway Disfigurement	-55% Cycle 37	26+	No change in R20 airway impedance. NRS-11 baseline score of 3 decreased to 0. Decrease in PI scores. Self-report GIC "tumor is less visible" and "appearance was huge before but now you barely notice it."	No SAEs; Grade 3 diarrhea; no dose reductions.	Tumor shrinkage is evident on photos. GIC with consistent reports of improvement by both patient and parent. Continued selumetinib at DCO. Inv. stated benefit.
	5 1/2	1 systemic	Orbit/Face; 111.2 mL	Vision Disfigurement	-32% Cycle 13	17	No change in exophthalmos. Parent reported decreased facial swelling.	No SAEs; no Grade 3-4 AEs; no dose reductions.	Parent report of reduced swelling did not correlate with obvious tumor shrinkage. Patient discontinued selumetinib for PD at Cycle 31. Inv. stated overall benefit.

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
(b) (6)	7	1 systemic	Abd/pelvis; 817 mL	Motor Bowel/bladder Pain Disfigurement	-36% Cycle 21	18+	Bladder dysfunction improved (6 to 4); improved ROM; decline in strength; GIC parent report indicates declines and improvements.	No SAEs. Grade 3 CPK elevation and dental caries. No dose reductions.	Variable reports of improvement and deterioration on GIC. Reports did not correlate with tumor volume changes. Patient continued selumetinib at DCO, but inv. stated that patient had not experienced benefit.
	8	2 systemic	Abd/pelvis/ext 1736 mL	Motor Bowel/bladder Pain Disfigurement	-35% Cycle 25	21+	Improved NRS-11 scores and PI index; improvements in bowel function; Increased ROM; variable strength results; patient report on GIC of improvement	No SAEs; no Grade 3-4 AEs; no dose reductions.	Patient appears to have improvement in more than one tumor related morbidity that correlated well with tumor volume reduction. Continued on selumetinib at DCO. Inv. stated benefit.
	9	None	Neck/trunk; 492 ML	Airway Disfigurement	-27%; Cycle 25	21+	Improved R20 AW impedance; FEV1 improved but was WNL at baseline. Self-report on GIC Cycle 13: "My tumor got smaller. It doesn't hurt anymore; I can move my neck more than I used to." Parent report was consistent.	No SAEs; no Grade 3-4 AEs; no dose reductions.	Overall improvement based on GIC patient and parent reports. Modest improvements in FEV1 and airway obstruction measures. Continued on selumetinib at DCO. Inv. stated benefit.

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
(b) (6)	16	1 prior systemic	Neck/trunk; 671 mL	Airway Motor Disfigurement	-25% Cycle 21	17+	No change in airway measures. No change in ROM or strength. NRS-11 baseline of 5 decreased to 0 during study. Self-report GIC: less pain and increased mobility of neck. Parent reports less pain complaints.	SAE of influenza and fever. No other Grade 3 events. No dose reductions.	No change in objective measures for airway and ROM and strength. Patient and parents reported improvement. Continued on selumetinib at DCO. Inv. stated no benefit.
	14	2 surgeries 1 systemic	Orbit 17.3 mL	Disfigurement	-34% Cycle 21	22+	No photos available. Patient and parent report tumor shrinkage on GIC. Pain decreased from baseline of 4 to 0 on NRS-11.	No SAEs; no Grade 3-4 AEs; no dose reductions.	Improvements noted in GIC reporting. No photos provided. Pain improved. Continued on selumetinib at DCO. Inv. stated benefit.
	6	1 surgery 1 systemic	Head/neck/chest 1630 mL	Airway Motor Pain Disfigurement Spinal cord compression	-29% Cycle 17	25+	Improvement in sleep disturbance. FEV1 fluctuated but always WNL. No change in R20 airway impedance. No change in ROM or strength. Pain scores improved at Cycle 5, and patient stopped regular opioid use by Cycle 5. Parent reports of less head tilt and improved sleeping. Later, parents	No SAEs; no Grade 3-4 AEs; no dose reductions.	Objective measures did not change substantially. Pain seems to have improved. Inconsistent reporting regarding sleep. The photos show obvious improvements in discoloration of skin over tumor but more subtle changes in tumor size. Continued on selumetinib at DCO. Inv. stated benefit.

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
							stated sleep remains problematic.		
(b) (6)	11	1 surgery 3 systemic	Neck/chest 3820 mL	Airway Motor Bowel/bladder Disfigurement	-25% Cycle 17	8	Tracheostomy present at baseline so no PFTs. No change in ROM. Parent report improved mobility. Pain appeared to increase during study.	Serious Gr 4 pressure ulcer with associated osteomyelitis led to DC.	Limited clinical outcomes results and toxicity considered related to selumetinib. Reviewer agrees with inv that patient did not appear to have had clinical benefit.
	6	2 surgeries	Abd/pelvis 322 mL	Motor Bowel/bladder Pain Disfigurement	-28% Cycle 17	19+	Decreased ROM. Improved strength. No change in incontinence. Improved PI at one year, but increased pain at 2 year mark and required surgical intervention for scoliosis.	No SAEs; no Gr 3-4 AEs; no dose reductions.	Limited benefit for pain symptoms for first year of treatment. Other measures did not show improvement. Patient continued selumetinib at DCO, but inv. stated that patient had not experienced benefit.
	6	None	Abd/pelvis/ext 1267 mL	Motor Bowel/bladder Pain Disfigurement	-28.5% Cycle 17	12+	Improved strength. No change in ROM. Parent GIC: can walk longer without getting tired. Bladder dysfunction was mild at baseline (voiding increased) and this normalized.	No SAEs. Dose reduction for skin toxicity.	Patient seems to have had mild symptoms/ functional impairment at baseline. Parents considered treatment beneficial for pain. Continued selumetinib at DCO. Inv. stated benefit.
	17	1 surgery	Lower ext 871 mL	Motor Pain Disfigurement	-43% Cycle 17	16+	Baseline NRS-11 6 decreased to 0 by Cycle 25. Self and parent	No SAEs; no Grade 3-4 AEs;	Decreased pain correlated with tumor shrinkage. GIC reports

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
							report of tumor shrinkage, decreased pain and increased flexibility. Improved ROM. Strength unchanged.	no dose reductions.	consistent between parent and patients and suggest improvement in leg function. Continued selumetinib at DCO. Inv. stated benefit.
(b) (6)	10	2 surgeries 2 systemic	Neck/chest/ext 3314 mL	Airway Motor Pain Disfigurement Difficulty swallowing	-23% Cycle 9	7+	Pain improved from 3 to 0 on NRS-11. Discontinued Neurontin. FEV1 57% at baseline; improved to 65% but still below nl. Sleep disturbance occurred on study. Improved ROM. No change in strength.	SAEs of Grade 3 skin infection, fracture and hematoma. Grade 3 vomiting. No dose reductions.	Improvement in pain symptoms correlated with tumor shrinkage. PFTs mildly improved. Patient reported increased ROM and ability to dress independently. Continued selumetinib at DCO. Inv. stated benefit.
	11	1 surgery 1 systemic	Neck/chest 138 mL	Airway Motor Pain Disfigurement	-23% Cycle 21	12+	FEV1 below normal and decreased during first year with improvement in second year. No change in ROM. Pain scores fluctuated but patient was rating two PNs. Patient and parent reports of increased neck mobility.	No SAEs; no Grade 3-4 AEs; no dose reductions.	Self and parent reporting not consistent with ROM testing. Patient continued selumetinib at DCO, but inv. stated that patient had not experienced benefit.
	16	2 surgeries	Neck 689 mL	Airway Motor Disfigurement	-30.5% Cycle 17	14+	FEV1 normal at baseline and did not decline. Sleep disturbance at	No SAEs; Grade 3 syncope;	Improved pain and sleep symptoms correlated with tumor shrinkage.

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
							baseline was gone at Cycle 13. Improved pain from 3 to 0 on NRS-11.	no dose reductions.	Continued selumetinib at DCO. Inv. stated benefit.
(b) (6)	15 ½	None	Neck/chest 563 mL	Airway Motor Pain Disfigurement	-21% Cycle 25	3+	PFTs unchanged. ROM unchanged. Strength unchanged. NRS-11 score 1 to 0.	No SAEs; no Grade 3-4 AEs; no dose reductions.	Unclear benefit shown on measures tested. Continued selumetinib at DCO. Inv. stated benefit.
	6 ½	1 systemic	Neck/chest 1791 mL	Airway Motor Vision Disfigurement	-31.5% Cycle 17	16+	Tracheostomy dependent-no PFTs. Sleep disturbance unchanged. Right eye vision loss baseline-no VA testing. Parent GIC reports clear shrinkage. Parent states patient walks better and has increased head mobility.	SAEs of Gr 3 hypoxia and tracheitis (unrelated). No dose reductions.	Unclear benefit shown on measures tested. Parent reports are positive. Continued selumetinib at DCO. Inv. stated benefit.
	9	None	Neck/ext 1247 mL	Motor Disfigurement	-22% Cycle 9	24+	Improved ROM. No change in strength. NRS-11 score of 0 at baseline. PI index improved. Patient and parent report on GIC that tumor is "much improved."	No SAEs; Grade 3 syncope; no dose reductions.	GIC positive for both patient and parent. Continued selumetinib at DCO. Inv. stated benefit.
	9	2 systemic agents	Neck/chest/ext 624 mL	Motor Pain Disfigurement	-37.5% Cycle 9	17	Improved ROM and strength during first year. NRS-11 baseline of	No SAEs. Grade 3 paronychia;	Patient had 2 dose reductions and regrowth of tumor at Cycle 13 and

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
							8 improved to 0 at Cycle 5 and 13. GIC self-report indicates less tumor pain. Patient maintained on stable dose of gabapentin on study.	2 dose reductions due to paronychia	PD at Cycle 21. Pt discontinued selumetinib for PD. Inv. stated benefit.
(b) (6)	5	None	Abd/pelvis/ext 1041 mL	Motor Pain	-25% Cycle 9	24	Improved strength and ROM. PI not documented. GIC parent report indicated less pain and improved gait and able to sit without pain for longer time periods (school).	No SAEs; no Grade 3-4 AEs; no dose reductions.	Objective measures and parent reports indicate improvements that correlated with tumor volume reduction. Continued selumetinib at DCO. Inv. stated benefit.
	15	3 surgeries Radio-ablation 4 systemic	Head/neck/chest 2962 mL	Airway Motor Disfigurement	-32% Cycle 9	7	Improved ROM. Unchanged strength. Nonfunctional left lung baseline – no PFTs. Sleep disturbance developed on study. Self-report of improved breathing and tongue remaining in mouth while drinking.	SAE of MPNST Grade 3 hypoxia (unrelated)	Improved mobility but no change in strength. Airway function unchanged but patient reported easier breathing and parents reported increased stamina. Patient stopped drug at dx of MPNST and resumed selumetinib through EAP after surgical resection. Inv. stated benefit.
	15	1 systemic	Neck/chest/ abd/pelvis	Airway Motor	-29%	15+	FEV1 WNL at baseline but increased from	No SAEs; no Grade	Extent of tumor burden made pain assessments

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
			1824 mL	Pain Disfigurement			during study. Improved ROM. Unchanged strength. Improved NRS-11 and PI. Self report GIC of minimally improved tumor morbidity and much improved pain.	3-4 AEs; no dose reductions.	challenging in this patient, but patient and parent reports indicate improved pain. Gabapentin was used routinely at baseline and throughout study with NSAID use PRN. Continued selumetinib at DCO. Inv. stated benefit.
(b) (6)	6	1 surgery	Head/orbit 44.5 mL	Vision Disfigurement	-39% Cycle 13	19+	VA unchanged in left eye (near PN) but decreased in right eye. Improved exophthalmos. PI score improved. Parent indicated less tumor pain and much fewer calls home from school nurse regarding pain.	No SAEs. Grade 3 diarrhea. No dose reductions.	Vision and disfigurement morbidities appear to not have changed during study. Benefit noted most in parent reports of difference in pain during study. Continued selumetinib at DCO. Inv. stated benefit.
	4	1 surgery 1 systemic	Abd/pelvis 427 mL Pt also had an optic glioma.	Bowel/bladder Disfigurement	-36% Cycle 25	18+	Ureterostomy was in situ at baseline so urinary continence questions could not be addressed. Parents reported less bowel accidents at Cycle 9 (had been daily before	2 SAEs for Grade 3 UTI. No dose reductions.	Improved bowel continence by parent report. Photos seem to show tumor shrinkage in the buttock area relative to baseline. The patient's urologist and the Inv. stated benefit. Continued selumetinib at DCO.

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
							study). GIC was not completed.		
(b) (6)	13	1 systemic	Abd/pelvis/ext 548 mL	Motor Pain Disfigurement	-31% Cycle 17	11	No change in ROM. Strength unchanged at most assessments. Improved PI on self report but no on parent report. Self and parent GIC both reported improved pain and overall improved quality of life.	No SAEs; no Grade 3-4 AEs; no dose reductions.	Objective measures for motor did not show improvement. PI reports were inconsistent between patient and parent. GIC positive. Inv. stated benefit. Continued selumetinib at DCO.
	14	1 surgery 1 systemic	Head/orbit 146 mL	Pain Vision Disfigurement Swallowing difficulty	-36% Cycle 9	15+	No VA tested due to right eye enucleation. NRS-11 was 9 at baseline and decreased to 5. Self report PI improvement was not consistent with parent report. GIC indicated overall improvement for both patient and parent.	No SAEs. Gr 3 AST and lipase elevation. 2 dose reductions for AST/ALT increase.	Pain seems to have improved, but patient was taking pain medications routinely at baseline and during study. Inv. stated benefit. Continued selumetinib at DCO.

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Patient ID	Age (yrs)	Prior Therapy	PN location; volume	Morbidity Assignment	Best response; Cycle	DoR at DCO in months	Clinical Outcomes	Safety	Reviewer Comments
(b) (6)	8	3 surgeries 3 systemic	Head/neck/ext 574 mL	Disfigurement	-38% Cycle 21	18+	Trach-dep baseline, removed during study. VA abnormal at baseline and no change during study.	No SAEs. Grade 3 tracheitis, lung infection, hypoxia-all unrelated. No dose reductions.	Trach removal is clear benefit; no vision improvement or deterioration. Inv stated benefit. Patient continued selumetinib at DCO.
	11	3 systemic	Neck 80 mL	Airway Motor Disfigurement	-32% Cycle 9	19+	FEV1 WNL at baseline and improved during study. No change in sleep disturbance. No airway impedance results. No change in ROM. Small increase in strength. Parent and self-report GIC were positive-easier to wear dress shirts.	No SAEs; 1 Gr 3 fracture; no dose reductions.	Inv stated that CPAP settings were stable on treatment and had been increasing prior and that pharyngeal PN was less visible. GIC positive. Inv stated benefit. Patient continued selumetinib at DCO.

DOR: duration of response; DCO: data cutoff; Inv: Investigator; Ext: extremity; Abd: abdomen; ROM: range of motion; GIC: Global impression of change; PFT: pulmonary function test; VA: visual acuity; WNL within normal limits

IPR Data: FDA Assessment

Review of the IPRs allowed for a better characterization of the patient population, the types of functional impairments and symptoms patients were experiencing at enrollment, and potential selumetinib effects on clinical outcomes at the patient level.

Patients had substantial baseline morbidity related to PN. Many tumors were large and disfiguring, and tumors that were located in critical areas such as near the airway or orbit, even when relatively small in size, caused considerable functional morbidity for patients.

Among the patients who experienced an objective response per REiNS criteria, 88% (29/33) remained on selumetinib at DCO and appeared to have good tolerability. One additional patient, who discontinued selumetinib due to diagnosis of MPNST, resumed selumetinib under the expanded access program after completing MPNST treatment. Two patients who had an objective response discontinued for PD at Cycles 21 and 31 respectively. One patient discontinued due to adverse events.

There was further reduction in tumor volume after initial onset of response, with best overall response occurring later for most patients, often after Cycle 13.

There was a trend of tumor volume reduction associated with at least one improved clinical outcome in most patients who experienced a durable objective response during selumetinib treatment.

There was evidence of clear benefit in some cases (e.g., tracheostomy tube removal, FEV1 normalization, ROM increase with examples of associated functional improvements, increased bowel/bladder continence, pain decrease). However, in other patients, objective measures were not consistent with patient and/or parent reports of improvement or with tumor volume reduction timepoints.

Tumor-related disfigurement was present in 88% of patients. Changes in disfigurement were marginal as demonstrated in the photos provided for most patients. Any obvious improvement is noted in the table. However, patients and parents often reported improvement in tumor appearance as part of the GIC that were not obvious to the reviewer. Further, some patients reported changes in texture of the tumor or skin overlying the tumor that they considered important improvements but that were not evident on photos.

All SPRINT investigators were interviewed prior to submission of the NDA and asked to provide an assessment regarding the overall benefit of selumetinib for their patients. Among the 50 patients, 70% (35/50) were considered to have experienced clinical benefit based on the investigator's assessment. Of the 15 patients who were considered to not have experienced benefit, 5 had an objective response per REiNS criteria; investigators stated that there was

minimal improvement in clinical morbidity or the toxicities outweighed the benefits in these patients. Among the 17 patients who did not experience a radiographic objective response to selumetinib, 3 patients were considered by investigators to have had benefit with selumetinib treatment based on improved pain symptoms (n=2) and improved bladder continence (n=1).

8.1.7. Integrated Assessment of Effectiveness

Data:

See the Applicant's Position below.

The Applicant's Position:

Data from the SPRINT Phase II Stratum 1 study, supported by the SPRINT Phase I and Natural History studies, provide substantial evidence of effectiveness of selumetinib for the treatment of pediatric patients with NF1 and inoperable PN.

Objective Response

- Selumetinib demonstrated a confirmed ORR by NCI POB central analysis of 66.0% (95% CI: 51.2, 78.8), based on 33 responders from 50 evaluable patients in SPRINT Phase II Stratum 1. A further 4 (8.0%) patients had an unconfirmed PR. No patients had progression as their best response.
- Reduction in target PN volume was observed early, with almost all patients having a reduction in target PN volume by 4 cycles (i.e., pre-Cycle 5, median percentage change in target PN volume from baseline was -14.31% at this time point).
- High ORR irrespective of PN status at enrolment (progressive PN: ORR of 61.9%) suggesting that PN status at enrolment appears to be independent from response rate and, therefore, not predictive of selumetinib efficacy.
- Inclusion of all available data (regardless of schedule or treatment discontinuation) did not affect ORR (66.0%).
- Supportive ORR data from SPRINT Phase I (66.7% [16 of 24 patients]) confirmed the high ORR observed in SPRINT Phase II Stratum 1.

Duration of Response

- Responses occurred early and were durable.
 - Of the 33 responders in SPRINT Phase II Stratum 1, almost half (14 [42.4%] patients) had achieved a response ($\geq 20\%$ reduction in target PN volume from baseline) by 4 cycles (ie, pre-Cycle 5). In addition, by 8 cycles (ie, pre-Cycle 9), 72.7% of patients had achieved a response.
 - The median DoR from onset of response based on NCI POB central analysis was not reached in either the pivotal SPRINT Phase II Stratum 1 or supportive Phase I data.

- Of the 33 responders in SPRINT Phase II Stratum 1, the probability of remaining in response after 12 cycles, estimated using the Kaplan-Meier method, was 100%.
- Of the 16 responders in SPRINT Phase I, the estimated proportion of patients remaining in response after 52 cycles, estimated using the Kaplan-Meier method, was 100%.

Progression-free Survival

- Very few patients progressed in either SPRINT Phase II Stratum 1 (3 patients) or SPRINT Phase I (2 patients).
 - Median PFS was not reached in SPRINT Phase II Stratum 1. There was a very high probability (94.7% [95% CI: 80.6, 98.7]) of remaining without progressive disease after 2 years in SPRINT Phase II Stratum 1.
 - Median PFS was not reached in SPRINT Phase I.

Clinical Outcome Assessments

- Most patients experienced improvements in their COA scores as well as reduced target PN volume.
 - The mean reduction in pain intensity (2.07) achieved by pre-Cycle 13 was considered clinically meaningful. Pain palliation occurred early, within 2 to 4 months, for those patients experiencing pain at baseline (NRS-11 score ≥ 2) and was sustained over time. Additionally, patients and parents reported a reduction in pain interference over time.

Correlation of Changes in COA and Target PN Volume

- Strong correlations ($r=0.76$ [pre-Cycle 9] and 0.71 [pre-Cycle 25]) were detected between NRS-11 scores (patient score ≥ 2 at baseline) and percentage change in target PN volume. Based on the longitudinal analyses (after adjusting for age, number of morbidities and the baseline value of the clinical outcome), there was evidence of a meaningful correlation between percentage change from baseline in target PN volume and change in NRS-11 score ($p<0.001$).
- Weak correlations were detected between percentage change in PN volume and PII, PROMIS transformed scores, and ROM. Correlation analyses were impacted by the presence of patients who did not have the potential to improve by the recommended clinically meaningful threshold. Based on the longitudinal analyses (after adjusting for age, number of morbidities and the baseline value of the clinical outcome), a signal was also observed for parent-report PedsQL total ($p=0.033$).

External Control Data

Comparison with the external control data confirmed the clinical benefit observed with selumetinib in pediatric patients with NF1 and symptomatic, inoperable PN:

- Natural History study data indicate that the PN shrinkage observed in SPRINT Phase II Stratum 1 can be attributed to selumetinib, rather than the natural course of the disease. The adjusted mean annual growth rate was +21.3% (95% CI: 15.9, 26.8) per year in the Natural History study age-matched cohort compared with -16.9% (95% CI: -20.2, -13.5) per year in SPRINT Phase II Stratum 1.
- The PFS benefit of selumetinib treatment observed in SPRINT Phase II Stratum 1 was confirmed by the Natural History age-matched cohort as most patients in this cohort had progressed (76.1%), median PFS was 1.3 years (95% CI: 1.1, 1.6) with the probability of remaining without progressive disease after 2 years of 30.4% (95% CI: 21.0, 40.3).
- The PFS benefit of selumetinib treatment in observed in SPRINT Phase II Stratum 1 was confirmed by the placebo arm of tipifarnib Study 01-C-0222, (patients with progressive PN) where most patients in this control group had progressed (23 of 29 patients, 79.3%), median PFS was estimated as 1.0 year, with the probability of remaining without progressive disease after 2 years of 20.6% (95% CI: 7.7, 37.8).

In conclusion, selumetinib represents a substantial improvement over current clinical management options on clinically significant endpoints and would represent a clear clinical benefit for these patients with NF1 who have a high unmet need as there are no approved treatment options.

The FDA's Assessment:

The FDA generally agrees with the Applicant's summary of response rate and DOR data from SPRINT Phase II Stratum 1 and the consistency of responses across relevant subgroups of patients (e.g., baseline progressive or nonprogressive disease). The FDA reiterates that data from the NCI POB NF1 Natural History Study and the placebo arm of Tipifarnib Study 01-C-0222 was not independently confirmed. Given the heterogeneity in the patient population in measured and unmeasured factors (e.g., disease characteristics, patient characteristics, treatment characteristics, etc.), the FDA considered results from the external control studies to be supportive but inadequate for any comparative analyses.

FDA has the following additional summary comments:

SPRINT Phase II Stratum 1 enrolled 50 pediatric patients with NF1 and an inoperable PN that resulted in significant clinical morbidity. The ORR per NCI central review using REiNS criteria was 66% (33/50; 95% CI: 51, 79). All responses were confirmed PRs. Among the 33 responders, the median DOR was not reached, and the proportion of patients who experienced DOR $\geq$ 12 months was 82% (27/33). The ORR per ICR was 44% (22/50; 95% CI: 30, 59); the proportion of patients who experienced DOR $\geq$ 12 months per ICR was 59% (13/22). The FDA notes that the difference in ORR observed between the NCI central review and the ICR is in part due to tumor volume measurements for 6 patients that showed PN shrinkage between -19.2% and -19.9% as best objective response (i.e., not meeting the 20% threshold for PR).

Supportive response data was submitted for the 24 patients with NF1 PN enrolled in SPRINT Phase 1 and for 25 patients enrolled in SPRINT Phase II Stratum 2. The NCI central review of ORR for these cohorts was 67% (16/24; 95% CI: 45, 84) and 68% (17/25; 95% CI: 47, 85) respectively. All 16 of the 16 responders (100%) in SPRINT Phase 1 trial and 12 of the 17 responders (71%) in SPRINT Phase II Stratum 2 had a duration of response $\geq$ 12 months from the onset of response. These data support the efficacy of selumetinib in the intended indication.

The response rate results for SPRINT Phase II Stratum 1 were considered in the context of clinical outcomes for patients during treatment including the effects on PN-related symptoms and functional impairments. Acknowledging the limitations of the single arm design and the small sample sizes of patients assessed for each PN-related morbidity subset, there was a general trend of tumor volume reduction that was associated with at least one improved clinical outcome in most patients who experienced a durable response during selumetinib treatment. The effect on the associated morbidity appeared to be similarly durable. See Section 8.1.6, Additional Efficacy Considerations.

8.2. Review of Safety

8.2.1. Safety Review Approach

The Applicant's Position:

The principal source of data supporting the safety evaluation of selumetinib in the proposed indication is based on an analysis of the Phase II Stratum 1 data of the SPRINT study. Supportive safety data from the Phase I data of the SPRINT study is presented individually and also pooled with the Phase II Stratum 1 data. The pediatric safety data populations are as follows:

- **Pivotal pediatric safety data (Phase II Stratum 1 of SPRINT):** 50 pediatric patients aged $\geq$ 3 and $\leq$ 18 years (able to swallow whole capsules) with NF1 and inoperable PN and PN related morbidity at enrolment who received at least 1 dose of selumetinib 25 mg/m² BID based on BSA. This safety population informs adverse drug reactions (ADRs) in the proposed label.
- **Supportive pediatric safety data:**
 - Phase I of SPRINT: 24 pediatric patients aged $\geq$ 3 and $\leq$ 18 years (able to swallow whole capsules) with NF1 and inoperable PN and received at least 1 dose of selumetinib (20, 25 or 30 mg/m² BID based on BSA). This study is used to provide further safety information towards the evaluation of the safety profile of selumetinib in pediatric patients.
 - Pediatric safety pool: 74 pediatric patients who received selumetinib (all doses included) in the SPRINT Phase II Stratum 1 and Phase I studies. This pool is used

to provide a greater population size for the characterization of the selumetinib safety and tolerability profile, and to ensure that safety events were evaluated in all available data from selumetinib treated pediatric patients. A subset of this pool was for patients who received selumetinib 25 mg/m² BID per initial dose assignment in either phase (N=56).

Further support for the evaluation of the safety of selumetinib as a monotherapy treatment is provided by pooled safety data from adult patients with cancer treated with selumetinib monotherapy in 7 completed AstraZeneca-sponsored studies. Non AstraZeneca-sponsored studies and AstraZeneca sponsored studies of selumetinib in combination with other anti-cancer agents are excluded from the selumetinib Adult monotherapy pool. The safety profile of selumetinib monotherapy in adult patients has been well characterized across multiple studies and is in line with the established safety profile of the MEK inhibitor class effects, including those seen in currently approved MEK inhibitors trametinib, cobimetinib and binimetinib.

- **Supportive adult safety data**

- Adult monotherapy pool: 347 adult patients in which 79 patients received selumetinib capsules (hyd-sulfate) and 268 patients received selumetinib free base. These data supplement the pivotal and supportive pediatric data and provide a larger overall population for a robust evaluation and characterization of the safety and tolerability profile of selumetinib.

The pediatric safety data have not been pooled with safety data from AstraZeneca-sponsored studies of selumetinib monotherapy in adult cancer patients due to differences in patient populations, dose levels and exposure.

Additional supportive data are provided from the safety populations of the following studies for the evaluation of potential and identified risks:

- 12 Phase I Clinical Pharmacology studies (approximately 380 healthy adult volunteers)
- Ongoing Early Access Program (EAP; (b) (4)/D1346R00002, DCO: 31 January 2019): 166 patients aged 3 years and above at enrolment with NF1-related PN.
- Pediatric externally-sponsored research (ESR) studies (DCO: 31 January 2019). Serious adverse events (SAEs) are reported for 291 pediatric patients who have enrolled in externally-sponsored studies evaluating selumetinib in a range of indications.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the primary and supportive safety datasets included in the NDA. The FDA has the following additional comments regarding the approach to the safety review:

The pediatric safety pool included 74 patients with NF1 and PN treated with single-agent

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selumetinib administered at doses ranging from 20 mg/m² to 30 mg/m² twice daily during the SPRINT trial. The on-treatment safety monitoring periods for the SPRINT trial were from the time of first dose to 30 days after the last dose of selumetinib. The data cut-off date for the safety results from SPRINT was June 29, 2018. Most of the patients in SPRINT (N=56) received the intended marketing dose of 25 mg/m² twice daily. Since the study populations and the AE profiles were similar between the SPRINT Phase II Stratum 1 dataset (N=50) and the pediatric pool (N=74), the FDA focused on the larger pediatric pool for key safety analyses that would inform the warnings and precautions included in the product label.

The FDA independently reviewed exposure and safety data from SPRINT Phase II Stratum 1 (N=50) and from the pediatric pool (N=74). The FDA did not analyze exposure and AE rates by dose cohorts in SPRINT Phase 1 (20 mg/m², 25mg/m², 30 mg/m²) due to the small sample sizes of the subgroups receiving doses higher than (N=6), or lower than (N=12), the recommended dose in the label. AE rates in these dosing subgroups were not considered to be informative of the overall safety profile of selumetinib in the study population. It will be noted in the review if important AEs that are possibly dose-related occurred at a dose higher than the labeled dose.

Given the limited sample size of the pediatric pool (N=74), the FDA additionally reviewed safety data from the “adult monotherapy pool” of 347 adult patients who received single agent selumetinib across seven adult oncology trials. During the review, the FDA noted that the safety profiles of the two selumetinib formulations represented in this pool [hyd-sulfate capsule (N=79); free base oral suspension (N=268)] were different. Patients receiving the capsule formulation had a greater incidence rate of SAEs (33% vs. 24%), AEs $\geq$ Grade 3 (60% vs. 43%) and discontinuations due to AEs (29% vs. 10%) than those who received the free base formulation. The FDA clinical pharmacology team reviewed data comparing the relative bioavailability between the two formulations in adult patients with advanced cancers enrolled in Study D1532C00005. PK parameters of AUC and C_{max} were compared and showed that the capsule has ~2-fold AUC and 2.5-fold C_{max} as compared to that of the free base. Since the two formulations are not bioequivalent and the capsule formulation is intended for marketing and exhibited more than 2-fold increased drug exposure in plasma, the FDA focused on the cohort of 79 adult patients who received the hyd-sulfate capsule for supportive safety data. The larger safety database was used to identify rare adverse drug reactions that may not have been identified in the smaller dataset. Additionally, the FDA requested and reviewed safety analyses of the Applicant’s global database of selumetinib monotherapy and combination studies for specific MEK inhibitor class safety signals.

Regarding the data from the ongoing selumetinib expanded access program for NF1 PN (N=166 as of January 2019) and from non-AstraZeneca sponsored pediatric studies of selumetinib in multiple tumor types (N=291 as of January 2019), the FDA notes that determining true AE incidence rates from analysis of these datasets is not possible due to variable reporting requirements between countries (for the expanded access program), data collection methods,

and continued accrual in ongoing studies. Further, these datasets had missing elements for a substantial number of the events such as AE duration, toxicity grade, action taken in response to the event, and outcomes. The FDA reviewed the SAE datasets for these studies to further assess known, but less common, safety signals associated with the MEK inhibitor drug class and to identify any new safety signals that may not have been observed in the SPRINT pediatric pool.

The FDA agreed with the Applicant's plan to not pool the adult and pediatric data given the differences in dose (the pediatric MTD is approximately 60% of the adult MTD), exposure (the median exposure time to selumetinib was much longer in the pediatric data relative to the adult data), and study populations (pediatric patients with underlying NF1 and a benign tumor versus adult patients with refractory cancer diagnoses).

An updated safety analysis with corresponding datasets (data cut-off date of March 29, 2019), for SPRINT Phase II Stratum 1 to supplement the SCS as part of the 90-day safety update was submitted on December 12, 2019. The safety update report included an additional 9 months of exposure for this cohort. Key safety analyses from the updated dataset were verified by the reviewer for the purpose of assessing safety with longer exposures to selumetinib. The 90-day safety update did not identify new safety signals not already discussed in this review.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Exposure for the safety populations is presented for the safety analysis set which includes all patients who received at least 1 dose of selumetinib.

In the pivotal SPRINT Phase II Stratum 1, median total exposure to selumetinib was 2.2 years (801.5 days [26.3 months], range 28 to 1053 days). Median actual exposure of 2.0 years (721.5 days [23.7 months], 26 to 1022 days) was similar to median total exposure indicating selumetinib dose interruptions were short for at least half of the patients enrolled in the study. Most patients in the SPRINT Phase II Stratum 1 received ≥ 24 to ≤ 36 months (66.0% patients) total treatment with selumetinib, the remaining patients received ≥ 12 to ≤ 24 months (22.0% patients) or received < 12 months (6.0%) total treatment with selumetinib.

The median and duration of exposure in the Pediatric pool (855.5 days, range 28 to 2169 days) was higher than in SPRINT Phase II Stratum 1 data as it was influenced by the longer exposure to selumetinib in the SPRINT Phase I data (median total treatment duration of approximately 4.4 years [1606 days]). Most patients in the supportive SPRINT Phase I data had received ≥ 48 to ≤ 60 months (42.0% patients) treatment with selumetinib, with 3 patients (12.5%) receiving > 60 months of selumetinib treatment.

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Longer exposure to selumetinib in the supportive SPRINT Phase I data contributes information towards the safety profile over time.

Table 40 SPRINT Phase II Stratum 1 and the Pediatric Pool: Duration of Selumetinib Exposure (Safety Analysis Set)

		Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Total treatment duration (days) ¹	Mean (SD)	725.7 (253.50)	819.2 (362.54)	1519.2 (533.11)	1598.3 (13.84)	1380.0 (700.01)	978.2 (506.14)
	Median (min-max)	801.5 (28-1053)	818.5 (28-1617)	1738.5 (158-2169)	1597.0 (1583-1617)	1409.5 (500-2131)	855.5 (28-2169)
	Total treatment years	99.3	125.6	49.9	26.3	22.7	198.2
Total treatment duration (months) ²	Mean (SD)	23.8 (8.33)	26.9 (11.91)	49.9 (17.51)	52.5 (0.45)	45.3 (23.0)	32.1 (16.63)
	Median (min-max)	26.3 (1-35)	26.9 (1-53)	57.1 (5-71)	52.5 (52-53)	46.3 (16-70)	28.1 (1-71)
Total treatment duration (months) ²	<12	6 (12.0)	6 (10.7)	1 (8.3)	0	0	7 (9.5)
	≥12 to ≤24	11 (22.0)	11 (19.6)	0	0	1 (16.7)	12 (16.2)
	>24 to ≤36	33 (66.0)	33 (58.9)	1 (8.3)	0	2 (33.3)	36 (48.6)
	>36 to ≤48	0	0	2 (16.7)	0	0	2 (2.7)
	>48 to ≤60	0	6 (10.7)	5 (41.7)	6 (100.0)	1 (16.7)	12 (16.2)
>60	0	0	3 (25.0)	0	2 (33.3)	5 (6.8)	
Actual treatment duration (days) ³	Mean (SD)	669.6 (240.98)	755.7 (339.02)	1384.0 (506.03)	1473.3 (54.84)	1189.5 (620.91)	892.7 (461.43)
	Median (min-max)	721.50 (26-1022)	742.5 (26-1539)	1468.5 (139-1995)	1488.5 (1389- 1539)	1204.5 (424- 1904)	777.8 (26-1995)
	Total treatment years	91.7	115.9	45.5	24.2	19.5	180.9
Actual treatment duration (months) ²	Mean (SD)	22.0 (7.92)	24.8 (11.14)	45.5 (16.63)	48.4 (1.80)	39.1 (20.40)	29.3 (15.16)
	Median (min-max)	23.7 (1-34)	24.4 (1-51)	48.2 (5-66)	48.9 (46-51)	39.6 (14-63)	25.6 (1-66)

Table 40 SPRINT Phase II Stratum 1 and the Pediatric Pool: Duration of Selumetinib Exposure (Safety Analysis Set)

		Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Actual treatment duration (months) ²	<12	6 (12.0)	6 (10.7)	1 (8.3)	0	0	7 (9.5)
	≥12 to ≤24	21 (42.0)	21 (37.5)	0	0	2 (33.3)	23 (31.1)
	>24 to ≤36	23 (46.0)	23 (41.1)	1 (8.3)	0	1 (16.7)	25 (33.8)
	>36 to ≤48	0	2 (3.6)	4 (33.3)	2 (33.3)	0	6 (8.1)
	>48 to ≤60	0	4 (7.1)	4 (33.3)	4 (66.7)	2 (33.3)	10 (13.5)
	>60	0	0	2 (16.7)	0	1 (16.7)	3 (4.1)

¹ Total treatment duration (days)=last dose date where dose >0 mg to first dose date+1.

² One month = 30.4375 days.

³ Actual treatment duration (days)=sum of days of study dose administered.

BID Twice daily; Max Maximum; Min Minimum; SD Standard deviation.

Rows are cumulative and patients are included if they have taken selumetinib treatment up to and including that month.

Source: Table 2.7.4.2.1.1 of the ISS Pediatric pool, Module 5.3.5.3.

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In the Adult monotherapy pool, the median total duration of exposure to selumetinib was 63.0 days (2.1 months, range 0 to 14 months), with most patients (97.1%) having had <12 months and 10 patients (2.9%) having had ≥12 to ≤24 months dosing with selumetinib. Exposure was shorter in the Adult monotherapy pool compared to the Pediatric pool due to the differences in patient populations as in adult oncology studies patients were predominantly late-line patients, the majority of whom progressed whilst on study and hence discontinued treatment.

Table 41 Adult Monotherapy Pool: Duration of Selumetinib Exposure (Safety Analysis Set)

		Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Adult Monotherapy Pool (N=347)
Total treatment duration (days) ^a	Mean (SD)	75.3 (64.45)	96.5 (90.18)	91.7 (85.39)
	Median (min-max)	57.0 (1-329)	64.5 (1-436)	63.0 (1-436)
	Total treatment years	16.3	70.8	87.1
Total treatment duration (months) ^b	Mean (SD)	2.5 (2.12)	3.2 (2.96)	3.0 (2.81)
	Median (min-max)	1.9 (0-11)	2.1 (0-14)	2.1 (0.14)
Total treatment duration (months) ^b	<12	79 (100)	258 (96.3)	337 (97.1)
	≥12 to ≤24	0	10 (3.7)	10 (2.9)
Actual treatment duration (days) ^{b,c}	Mean (SD)	70.6 (62.80)	93.1 (87.44)	88.0 (82.93)
	Median (min-max)	50.0 (1-324)	64.0 (1-436)	62.0 (1-436)
	Total treatment years	15.3	68.3	83.6
Actual treatment duration (months) ^c	Mean (SD)	2.3 (2.06)	3.1 (2.87)	2.9 (2.72)
	Median (min-max)	1.6 (0-11)	2.1 (0-14)	2.0 (0-14)
Actual treatment duration (months) ^b	<12	79 (100)	260 (97.0)	339 (97.7)
	≥12 to ≤24	0	8 (3.0)	8 (2.3)

Table 41 Adult Monotherapy Pool: Duration of Selumetinib Exposure (Safety Analysis Set)

		Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Adult Monotherapy Pool (N=347)
Relative dose intensity (RDI)	Mean (SD)	86.6 (16.97)	92.6 (14.77)	91.2 (15.48)
	Median	94.0	100.0	100.0
	Min	27	13	13
	Q1	80.0	94.6	87.9
	Q2	100.0	100.0	100.0
	Max	100	100	100

¹ Total treatment duration (days) = last dose date where dose >0 mg - first dose date +1.

² One month = 30.4375 days.

³ Actual treatment duration (days) = total treatment duration (days) - total duration of dose interruptions (days). RDI is the percentage of the actual cumulative dose delivered up to the actual last day of dosing relative to the intended cumulative dose up to the actual last day of dosing.

BID Twice daily; Max Maximum; Min Minimum; RDI Relative dose intensity; SD Standard deviation; Q1 Lower quartile; Q2 Middle quartile.

Source: Table 2.7.4.2.1.2 and Table 2.7.4.2.3 of the ISS Adult monotherapy pool, Module 5.3.5.3.

The Applicant's Position:

The overall extent and duration of exposure in the pivotal SPRINT Phase II Stratum 1 data, supported by the Phase I data and Pediatric pool is considered sufficient to adequately assess the safety profile of selumetinib for the proposed indication, given that selumetinib has been extensively studied in adult patients.

The FDA's Assessment:

The FDA agrees with the exposure data presented in Table 40 and Table 41 for SPRINT Phase II Stratum 1 (N=50), the pediatric pool (N=74), the adult hyd-sulfate pool (N=79) and the adult monotherapy pool (n=347).

The pediatric exposure data demonstrate a relatively long duration of treatment with a median actual exposure time of 25.5 months and nearly 60% of patients receiving selumetinib for more than two years at DCO. This is partly due to the benign condition that was studied and the potential need for chronic dosing for sustained effect given the observed regrowth of tumors during dose interruptions. Although the pediatric pool includes a relatively small sample size, the FDA considered the exposure data sufficient to assess the general safety profile of selumetinib in the intended population.

The supportive adult safety data in the application is limited by short selumetinib exposure times. The median actual treatment duration for the 79 patients receiving the relevant hyd-sulfate capsule formulation was 50 days (range 1 to 324 days) with approximately 80% exposed

for less than 3 months. This limitation was considered during the review, and the FDA requested that the Applicant submit additional safety analyses of the selumetinib global database and expanded access program for signals that may not have been identified in the adult data available in the original NDA. The Applicant was able to provide these additional analyses, and these are summarized in relevant sections of the review.

Relevant characteristics of the safety population:

Data:

See the Applicant's Position below.

The Applicant's Position:

The demographic and disease characteristics of patients recruited to the pediatric SPRINT Phase II Stratum 1 and supportive SPRINT Phase I populations were representative of the intended target population to be treated in clinical practice. The entry criteria were designed to include patients relevant to the target population and exclude patients whose participation would have been inappropriate for safety reasons.

Similarly, the demographic and disease characteristics of the adult patients in studies of cancer where also in line with the entry criteria of these studies. Clearly, the pediatric patients in the SPRINT Phase II Stratum 1 and Phase I populations with NF1 and adult studies in cancer differ in terms of demographic (e.g., age), and baseline characteristics, which should be taken into consideration when comparing the safety data from these populations. Despite the differences, the Adult monotherapy pool is still relevant to support the safety populations from the pediatric SPRINT study as it allows a better and clearer understanding of the safety profile of selumetinib through the identification and delineation of the ADRs associated with selumetinib compared to those events related to other factors related to demographics, baseline characteristics and underlying disease. Given the large differences between the 2 populations (age, underlying disease, medical history, prior therapies etc.), AEs occurring commonly in both populations will give stronger confidence and confirmation of being caused by selumetinib and not due to population-related factors. The presentation of the safety profiles in both populations will also allow a better characterization of selumetinib ADRs, their patterns (incidence, severity, duration etc.), their management and the selumetinib risk mitigation measures and whether a modification of these measures is required in different populations.

The FDA's Assessment:

The FDA refers to Section 8.2.1 for a description of the safety datasets included in the NDA. The FDA agrees that the baseline demographic and disease characteristics of the patients enrolled

in SPRINT are consistent with the intended population for use. The FDA also agrees with not pooling the pediatric and adult data for reasons already discussed.

Although the FDA agrees that similar types and frequencies of adverse reactions occurring in both the pediatric and adult populations could increase the confidence in determining selumetinib relatedness, it is important to note that AEs that occurred with relatively increased frequency or severity in the pediatric population as compared to the adult population are not necessarily less likely to be related to selumetinib. Confounding variables include short exposure times in the adult dataset, the relatively small sample size of adult patients receiving the relevant (and more bioavailable) capsule formulation, and potential differences in tolerability based on having an underlying benign or malignant condition. Further, while the adult population may be more vulnerable to developing certain adverse reactions due to age, prior therapy, and underlying cancer, absence of specific safety signals in the pediatric data does not indicate that pediatric patients are not at risk for these adverse reactions.

Adequacy of the safety database:

Data:

See the Applicant's Position below.

The Applicant's Position:

Overall, the safety data allows for an informed assessment of the safety profile of selumetinib and a judgment of the benefit-risk in pediatric patients aged 3 years and above, with NF1 and symptomatic, inoperable PN.

The FDA's Assessment:

The primary safety data from SPRINT, the supportive adult monotherapy pooled data, the supplemental data from the selumetinib expanded access program and externally-sponsored pediatric selumetinib studies and the additional safety analyses of the Applicant's global selumetinib database submitted during the review allowed for an informed risk assessment of selumetinib in the intended indication. The longer term safety profile of selumetinib in the intended population will require further evaluation in the post-marketing setting.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Not applicable.

The Applicant's Position:

The NDA submission contains all required components of the electronic common technical document (eCTD). The overall quality and integrity of the application is adequate.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. See Section 8.1.2 *Data Quality and Integrity* for the FDA's assessment of overall data quality and integrity in the NDA.

Categorization of Adverse Event

Data:

The number and proportion of patients who had at least 1 AE in any category in SPRINT Phase II Stratum 1, the Pediatric pool, or the Adult monotherapy pool are summarized in Table 42 and Table 43, respectively.

SPRINT Phase II Stratum 1 and the Pediatric Pool

In the Pediatric pool, 73/74 (98.6%) patients had at least 1 AE (Table 42); regardless of severity, AEs were assessed by the investigator as causally-related to selumetinib in 73 (98.6%) patients. Approximately two-thirds of patients (50 [67.6%]) had an AE of Grade ≥ 3 , and 17 (23.0%) patients experienced an SAE. No patients died due to an AE. AEs resulting in permanent discontinuation of selumetinib (DAEs) were reported in 9 (12.2%) patients, 58 (78.4%) patients had AEs leading to dose interruption, and 24 (32.4%) patients had AEs leading to dose reduction of selumetinib.

The overall incidence of AEs in each category were similar for both the SPRINT Phase II Stratum 1 and Pediatric pool, however, the incidence of AEs leading to dose reduction were higher in the Pediatric pool than the SPRINT Phase II Stratum 1 population (32.4% vs. 24.0%, respectively). This can be attributed to the inclusion of the Phase I dose escalation study in the Pediatric pool.

Table 42 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events in Any Category (Safety Analysis Set)

	Number of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Any AE	49 (98.0)	55 (98.2)	12 (100)	6 (100)	6 (100)	73 (98.6)
Any AE causally related to selumetinib ^b	49 (98.0)	55 (98.2)	12 (100)	6 (100)	6 (100)	73 (98.6)
Any AE of CTCAE Grade ≥3	31 (62.0)	36 (64.3)	8 (66.7)	5 (83.3)	6 (100)	50 (67.6)
Any AE of CTCAE Grade ≥3 causally related to selumetinib ²	19 (38.0)	22 (39.3)	5 (41.7)	3 (50.0)	5 (83.3)	32 (43.2)
Any AE with outcome of death	0	0	0	0	0	0
Any AE with outcome of death causally related to selumetinib ²	0	0	0	0	0	0
Any SAE (including events with outcome=death)	12 (24.0)	14 (25.0)	2 (16.7)	2 (33.3)	1 (16.7)	17 (23.0)
Any SAE (including events with outcome=death), causally related to selumetinib ²	6 (12.0)	7 (12.5)	1 (8.3)	1 (16.7)	0	8 (10.8)
Any AE leading to discontinuation of selumetinib	6 (12.0)	6 (10.7)	1 (8.3)	0	2 (33.3)	9 (12.2)
Any AE leading to dose reduction of selumetinib	12 (24.0)	15 (26.8)	5 (41.7)	3 (50.0)	4 (66.7)	24 (32.4)
Any AE leading to dose interruption of selumetinib	40 (80.0)	45 (80.4)	8 (66.7)	5 (83.3)	5 (83.3)	58 (78.4)
Any AE leading to dose modification	40 (80.0)	45 (80.4)	8 (66.7)	5 (83.3)	5 (83.3)	58 (78.4)
Any AEs of special interest	49 (98.0)	55 (98.2)	12 (100)	6 (100)	6 (100)	73 (98.6)
Any AEs of special interest, causally related to treatment ²	49 (98.0)	55 (98.2)	12 (100)	6 (100)	6 (100)	73 (98.6)
Any AEs of special interest of CTCAE Grade 3 or higher	11 (22.0)	14 (25.0)	3 (25.0)	3 (50.0)	5 (83.3)	22 (29.7)

Table 42 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events in Any Category (Safety Analysis Set)

	Number of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Any AEs of special interest of CTCAE Grade 3 or higher, causally related to treatment ²	9 (18.0)	12 (21.4)	2 (16.7)	3 (50.0)	4 (66.7)	18 (24.3)
AEs with a start date >30 days after discontinuation of selumetinib	4 (8.0)	4 (7.1)	0	0	1 (16.7)	5 (6.8)

¹ Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

² As assessed by the investigator.

Includes adverse events with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

CTCAE version 4.0.3, MedDRA version 21.0.

AE Adverse event; BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities;

SAE Serious adverse event.

Source: Table 2.7.4.3.1.1.1.1 of the ISS Pediatric pool, Module 5.3.5.3.

Adult Monotherapy Pool

In the Adult monotherapy pool, 329 patients (94.8%) had at least 1 AE (Table 43); regardless of severity, AEs were assessed by the investigator as causally-related to selumetinib in 309 patients (89.0%). Approximately half of patients (163 [47.0%]) had an AE of Grade ≥ 3 , including 98 (28.2%) patients for whom the AE was considered causally related to selumetinib by the investigator. SAEs were reported for 91 (26.2%) patients, including 32 (9.2%) of patients for whom the SAE was considered by the investigator as causally related to selumetinib. Eleven patients (3.2%) died due to an AE (pulmonary embolism [3 patients], respiratory failure [2 patients] and acute kidney injury, cardio respiratory arrest, death, haemoptysis, intestinal perforation, and metastases to meninges [1 patient each]) Three (0.9%) patients died due to an AE considered causally related to selumetinib by the investigator (cardio-respiratory arrest, acute kidney injury, and respiratory failure, 1 patient each). DAEs were reported in 54 patients (15.6%), 94 patients (27.1%) had AEs leading to dose interruption, and 19 (5.5%) patients had AEs leading to dose reduction of selumetinib.

The overall incidence of AEs in each category were broadly similar for both the hyd-sulfate and free base sub-groups, however, the incidence of AEs of CTCAE Grade ≥ 3 , SAEs and DAEs were higher in the hyd-sulfate sub-group than the free base sub group:

- AEs of CTCAE Grade ≥ 3 : 59.5% for hyd-sulfate sub group vs. 43.3% for free base sub group.
- SAEs: 32.9% for hyd-sulfate sub-group vs. 24.3% for free base sub-group.
- DAEs: 29.1% for hyd-sulfate sub-group vs. 11.6% for free base sub-group.

Table 43 Adult Monotherapy Pool: Adverse Events in Any Category (Safety Analysis Set)

	Number (%) of Patients ¹		
	Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Total Selumetinib Adult Monotherapy Pool (N=347)
Any AE	77 (97.5)	252 (94.0)	329 (94.8)
Any AE causally related to selumetinib ²	70 (88.6)	239 (89.2)	309 (89.0)
Any AE of CTCAE Grade ≥3	47 (59.5)	116 (43.3)	163 (47.0)
Any AE of CTCAE Grade ≥3 causally related to selumetinib ²	22 (27.8)	76 (28.4)	98 (28.2)
Any AE with outcome=death	3 (3.8)	8 (3.0)	11 (3.2)
Any AE with outcome=death causally related to selumetinib ²	0	3 (1.1)	3 (0.9)
Any SAE (including events with outcome = death)	26 (32.9)	65 (24.3)	91 (26.2)
Any SAE (including events with outcome = death), causally related to selumetinib ²	7 (8.9)	25 (9.3)	32 (9.2)
Any AE leading to hospitalisation (including events with outcome = death)	22 (27.8)	56 (20.9)	78 (22.5)
Any AE leading to hospitalisation (including events with outcome = death), causally related to selumetinib ²	6 (7.6)	21 (7.8)	27 (7.8)
Any SAE causing discontinuation of selumetinib	7 (8.9)	20 (7.5)	27 (7.8)
Any SAE causing discontinuation of selumetinib, causally related to selumetinib ²	4 (5.1)	12 (4.5)	16 (4.6)
Any AE leading to discontinuation of selumetinib	23 (29.1)	31 (11.6)	54 (15.6)
Any AE leading to dose reduction of selumetinib	3 (3.8)	16 (6.0)	19 (5.5)
Any AE leading to dose interruption of selumetinib	18 (22.8)	76 (28.4)	94 (27.1)
Any AE leading to dose modification of selumetinib ³	19 (24.1)	83 (31.0)	102 (29.4)
Any other significant AEs ³		0	0
Any other significant AEs, causally related to treatment ^{2,4}		0	0
Any AEs of special interest	68 (86.1)	221 (82.5)	289 (83.3)
Any AEs of special interest, causally related to treatment ²	61 (77.2)	211 (78.7)	272 (78.4)
Any AEs of special interest of CTCAE Grade 3 or higher	11 (13.9)	47 (17.5)	58 (16.7)
Any AEs of special interest of CTCAE Grade 3 or higher, causally related to treatment ²	9 (11.4)	37 (13.8)	46 (13.3)

¹ Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Percentages are based on the total numbers of patients in the treatment group (N).

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² As assessed by the investigator.

³ Includes dose interruptions or reductions.

⁴ Significant AEs, other than SAEs and those AEs leading to discontinuation of study treatment, which are of particular clinical importance, were identified and classified as other significant AEs (OAEs).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

CTCAE version 4.0.3, MedDRA version 21.0.

AE Adverse event; BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities;

OAE Other significant AE; SAE Serious adverse event.

Source: Table 2.7.4.3.1.1.2.1 of the ISS Adult monotherapy pool, Module 5.3.5.3.

The Applicant's Position:

Most of the clinical methods used for assessment of safety and tolerability of selumetinib for labelling purposes were standard methods used in most clinical studies, including the reporting of AEs (irrespective of causality or seriousness), treatment-related AEs as judged by the investigator, AEs resulting in death, AEs resulting in permanent discontinuation, clinical laboratory data (clinical chemistry, haematology, and urinalysis), vital signs, physical examination finding, and ECGs (as clinically indicated). BSA was measured in the SPRINT study as dosing was based on BSA.

The definitions of AEs and SAEs were broadly equivalent between the NCI-sponsored SPRINT studies and the AstraZeneca-sponsored studies in the selumetinib Adult monotherapy pool and the clinical pharmacology studies. As the SPRINT study is a CTEP sponsored study coordinated by the NCI POB, it is not unexpected that some differences exist in the reporting of safety events between SPRINT and the AstraZeneca-sponsored studies included in the selumetinib Adult monotherapy pool. In SPRINT, CTCAE grade changes are reported as new AEs, whereas in AstraZeneca-sponsored studies CTCAE grade changes are reported under the same AE event, however, this has no impact on the interpretation of safety data as summary tables for interpretation have been produced at the patient level not at the event level. Furthermore, in the SPRINT study, the laboratory values outside of normal range are reported as an AE regardless of clinical significance, whereas in AstraZeneca-sponsored studies they are only reported as AEs if they are associated with clinical symptoms or judged clinically significant by the investigator or met seriousness criteria. Finally, multiple symptoms of a single diagnosis are all reported as separate AEs in the SPRINT study, whereas in AstraZeneca-sponsored studies the diagnosis is reported as an AE. The approach to AE reporting in SPRINT is conservative but advantageous to this small study of 50 patients as it will result in a high volume of AEs reported in the study database and will aid in building the clinical picture of every event.

In the SPRINT study, safety assessments were generally conducted at the respective investigator sites, however as some enrolled patients in the study lived some distance from the NCI POB, some study mandated evaluations (ie, medical history, physical examinations and laboratory evaluations) were conducted by local health care providers (HCPs). However, for patients enrolled at NCI POB, all LVEF assessments were performed at NCI POB and not at the local HCPs. The impact of the use of local HCPs on AE reporting was assessed by comparing the frequency of expected AEs (based on the selumetinib Investigator's Brochure) reported by the NCI POB site which used local HCPs to sites which did not use local HCPs.

Adverse events across the SPRINT study data, Pediatric pool and Adult monotherapy pool were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) (Version 21.0) and graded according to the NCI's common toxicity criteria (Version 4.03). For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades were used.

The FDA's Assessment:

The FDA agrees with the general methods used for the assessment of safety and tolerability of selumetinib and has verified the summary safety data presented in Table 42 for the SPRINT Phase II Stratum 1 and the pediatric pool cohorts, and the adult summary safety data presented in Table 43.

The FDA acknowledges the differences in AE reporting between the SPRINT trial (conducted by NCI) and the AstraZeneca-sponsored trials included in the adult safety pool as detailed in the Applicant's position statement and does not consider these differences to substantially impact the ability to reliably assess the safety profile of selumetinib in the intended indication.

With regard to the portion of safety data collected by local healthcare providers, the Applicant informed the FDA at a Type C meeting on July 18, 2018, that all of the SPRINT Phase II Stratum 1 patients enrolled at NCI (N=27) had at least one protocol-required safety evaluation performed by their local clinicians. No patient had a tumor-staging visit outside of the NCI POB. The FDA requested that the Applicant conduct and submit subgroup safety analyses for patients who received all study-related evaluations at one of clinical sites and for patients who had non-re-staging visits at local centers. There were no substantial differences between the AE profiles and no indication of AE underreporting for patients who underwent a portion of their safety assessments by local clinicians. See the FDA Assessment under Section 8.2.7.

The FDA also assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PTs) for 100% of the AE.xpt dataset for the pediatric pool. Of the 5,144 line listings in this dataset, the reviewer used matching of identical verbatim and MedDRA PTs (n=2,362 line listings) as well as manual evaluation of the remaining verbatim terms (n=2,782 line listings). The majority of nonidentical terms were due to spelling differences (diarrhoea versus diarrhea) similar conditions (e.g., dermatitis acneiform versus acneiform rash), laboratory abnormality abbreviations and descriptions, and verbatim terms that included descriptors (e.g., dry skin with peeling versus dry skin). Overall, the MedDRA PTs listed in the dataset adequately represented the verbatim terms from the CRFs.

Routine Clinical Tests

Data:

See the Applicant's Position below.

The Applicant's Position:

SPRINT

The following laboratory parameters were collected for both SPRINT Phase I and SPRINT Phase II Stratum 1:

- Hematology: Complete blood count with differential and platelets.

- Clinical chemistry: Electrolytes (including sodium, potassium, chloride, CO₂), calcium, phosphorus, magnesium, creatinine, blood urea nitrogen, glucose, AST, ALT, bilirubin, urinalysis, total protein, albumin, creatine phosphokinase (CPK), amylase, and lipase.

Samples for measurement of clinical laboratory parameters were collected at screening, at intervals throughout the treatment period and during the follow-up period. Any abnormal laboratory values were to be followed until return to baseline or stabilization of event. Laboratory assessments were performed by the hospital's local laboratory. If any abnormal laboratory result was considered clinically significant, the investigator was to provide details about the action taken with respect to the test drug and about the patient's outcome.

For the Pediatric pool, laboratory results were classified according to local reference ranges (ULN or lower limit of normal [LLN], as applicable and assigning low/high flags for haematology and clinical chemistry values). Grades were assigned based on laboratory values and CTCAE version 4.03 requirements only; clinical assessment of the CTCAE grade were not taken into account.

Selumetinib Adult Monotherapy Pool

Blood tests including standard hematology and clinical chemistry were performed according to the individual CSPs.

The selumetinib Adult monotherapy pooled analysis included the following laboratory parameters that were collected in all 7 adult monotherapy studies:

- Hematology: erythrocyte count; leukocyte count; absolute neutrophil count; absolute lymphocyte count; absolute monocyte count; absolute eosinophil count; absolute basophil count; hemoglobin; platelet count.
- Clinical chemistry: albumin; AST; ALT; alkaline phosphatase (ALP); creatinine; gamma glutamyltransferase; magnesium; potassium; sodium; total protein; total bilirubin; urea nitrogen; corrected calcium; calcium x phosphate.

For the adult monotherapy pool, laboratory results were classified according to the NCI CTCAE criteria Version 4.03 using project reference ranges (ULN or LLN, as applicable). Grades were assigned based on laboratory values and CTCAE requirements only; clinical assessment of the CTCAE grade were not taken into account. CTCAE grades were not defined for total protein, urea nitrogen, absolute eosinophil count, absolute basophil count, or absolute monocyte count.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the routine laboratory assessments collected during SPRINT and the adult clinical trials. The FDA notes that CPK was not routinely assessed in the adult trials as it was during SPRINT and that CPK elevation was a frequent laboratory abnormality and AE observed during SPRINT.

8.2.4. Safety Results

Deaths

Data:

Deaths: SPRINT Phase II Stratum 1 and the Pediatric pool

No deaths were reported in SPRINT Phase II Stratum 1 or SPRINT Phase I.

Deaths: Adult monotherapy pool

A total of 172 (49.6%) deaths occurred in the Adult monotherapy pool, including 152 (43.8%) deaths due to disease progression. The total number of patients who died due to an AE during selumetinib treatment (AEs with an onset date on or after the date of first dose and up to and including 30 days following last dose of selumetinib) was 11 (3.2%), including 3 (0.9%) patients for whom the AE leading to death was considered causally-related to selumetinib (Table 43). The number of patients who died due to an AE that started more than 30 days after permanent discontinuation of selumetinib was 3 (0.9%) (Table 44).

Overall, AEs with the outcome of death were most commonly reported in the system organ class (SOC) of Respiratory, thoracic and mediastinal disorders. Full details are presented in the individual study CSRs.

Of the 14 patients who died due to an AE:

- 11 patients had an AE leading to death during selumetinib treatment
 - In 7 (2.0%) patients, the investigator considered the death to be due to both the disease under investigation and a fatal AE.
 - In 4 (1.2%) patients, the death was considered to be as a consequence of the AEs alone
 - Of these 11 patients, 3 patients, all from the free base sub group, experienced an AE with the outcome of death that was assessed by the investigator as causally related to selumetinib.
- 3 patients had an AE leading to death with an onset date falling after 30 day follow up period.
 - In 2 (0.6%) patients, the investigator considered the death to be due to both the disease under investigation and a fatal AE.
 - In 1 (10.3%) patient, the death was considered to be as a consequence of the AEs alone.

Table 44 Adult Monotherapy Pool: Overview of Deaths from All Causes (Safety Analysis Set)

Category	N (%) of Patients		
	Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Total Selumetinib Adult Monotherapy Pool (N=347)
Total number of deaths	33 (41.8)	139 (51.9)	172 (49.6)
Death related to disease under investigation only	29 (36.7)	123 (45.9)	152 (43.8)
AE with outcome of death only	1 (1.3)	3 (1.1)	4 (1.2)
AE with outcome of death only (AE start date falling after 30 day follow up period)	1 (1.3)	0	1 (0.3)
Death related to disease and an AE with outcome of death	2 (2.5)	7 (2.6) ^a	9 (2.6) ^{1,2}
Other deaths ³	0	6 (2.2)	(1.7)

¹ Includes 2 patients with an AE start date falling after 30 day follow up period.

² Total number of patients who died due to disease and an AE with outcome of death occurring during selumetinib treatment or up to 30 days following the date of last dose of selumetinib is 7 patients.

³ Patients who died and were not captured in the earlier categories.

Death related to disease under investigation was determined by the investigator

Rows are mutually exclusive; patients were only reported in one category.

AE Adverse event; BID Twice daily

Source: Table 2.7.4.3.5.1.2 of the ISS Adult monotherapy pool, Module 5.3.5.3.

Causes of death due to AEs were generally consistent with those expected in patients with advanced cancer. AEs leading to death were mostly attributed either to underlying disease (7/11), concomitant medications or to the patient's medical history. In 3 cases the AE leading to death was causally attributed to selumetinib by the investigator, however, in these 3 cases, the reported preferred term (PT) leading to death was distinct and was not reported in more than 1 patient. All 3 cases had other confounding factors (see Table 45 for further details).

Table 45 Adult Monotherapy Pool: Listing of Fatal Adverse Events (Safety Analysis Set)

Patient Identifier	Sex (M/F)/ Age ¹ (Years)	Adverse Event (MedDRA Preferred Term)	Time from Start of Treatment to Onset of AE (Days)	Time to Death from First Dose / Last Dose (Days)	AE Possibly Causally Related to Selumetinib ²	Primary Cause of Death	Death Related to Disease Under Investigation?	Comments ³
Hyd-sulfate 75 mg BID (N=79)								
(b) (6)	F/63	Pulmonary embolism	18	32/32	No	Small intestine carcinoma metastatic	Yes	n/a
	F/66	Respiratory failure	83	85/3	No	Pneumonia aspiration	No	n/a
	F/65	Intestinal perforation	27	30/12	No	Pancreatic carcinoma metastatic	Yes	It is noted in the CSR that this case was incorrectly reported as an AE leading to death. The cause of death was due to disease progression. The AE of intestinal perforation was not considered by the investigator to be causally related to selumetinib.

Table 45 Adult Monotherapy Pool: Listing of Fatal Adverse Events (Safety Analysis Set)

Patient Identifier	Sex (M/F)/ Age ¹ (Years)	Adverse Event (MedDRA Preferred Term)	Time from Start of Treatment to Onset of AE (Days)	Time to Death from First Dose / Last Dose (Days)	AE Possibly Causally Related to Selumetinib ²	Primary Cause of Death	Death Related to Disease Under Investigation?	Comments ³
Free base 100 mg BID (N=268)								
(b) (6)	M/47	Cardio-respiratory arrest	40	40/2	Yes	Cardio-respiratory arrest	Yes	The patient had a history of hypertension (an independent risk factor for coronary artery disease) and was taking a number of medications, including anticonvulsants and methylphenidate (RITALIN™) ⁴ , which significantly confound the assessment of causality.
	M/69	Metastases to meninges	70	75/19	No	Metastases to meninges	Yes	n/a
	M/62	Death	17	17/6	No	Death	Yes	n/a
	F/69	Pulmonary embolism	55	58/1	No	Pulmonary embolism	No	n/a
	M/64	Pulmonary embolism	117	121/35	No	Pulmonary embolism	No	n/a

Table 45 Adult Monotherapy Pool: Listing of Fatal Adverse Events (Safety Analysis Set)

Patient Identifier	Sex (M/F)/ Age ¹ (Years)	Adverse Event (MedDRA Preferred Term)	Time from Start of Treatment to Onset of AE (Days)	Time to Death from First Dose / Last Dose (Days)	AE Possibly Causally Related to Selumetinib ²	Primary Cause of Death	Death Related to Disease Under Investigation?	Comments ³
(b) (6)	F/71	Acute kidney injury	6	8/2	Yes	Acute kidney injury	No	There were no laboratory data to confirm the stated diagnosis. Furthermore, there was some evidence of infection with flora noted in the urine and a raised white cell count, as well as hypotension. There was also no information regarding concomitant medication or medical history, which makes a causal assessment difficult. Clinical signs of lower limb oedema were present prior to death with evidence of abdominal ascites and widespread metastases. This combined with possible infection could provide a plausible alternative explanation of pre-renal failure.

Table 45 Adult Monotherapy Pool: Listing of Fatal Adverse Events (Safety Analysis Set)

Patient Identifier	Sex (M/F)/ Age ¹ (Years)	Adverse Event (MedDRA Preferred Term)	Time from Start of Treatment to Onset of AE (Days)	Time to Death from First Dose / Last Dose (Days)	AE Possibly Causally Related to Selumetinib ²	Primary Cause of Death	Death Related to Disease Under Investigation?	Comments ³
(b) (6)	F/33	Respiratory failure	19	24/19	Yes	Respiratory failure	Yes	The patient's underlying NSCLC combined with a pre-existing history of pericardial and pleural effusion, and pulmonary embolism with proven recurrence on this occasion may provide an alternative explanation for the patient's shortness of breath/dyspnoea, respiratory failure and eventual death. The recurrent pulmonary embolism in a NSCLC patient with known thrombophilia and disease progression would seem a probable alternative explanation for the event.
(b) (6)	M/64	Haemoptysis	68	69/3	No	Haemoptysis	Yes	n/a

¹ Age=at informed consent.

² As assessed by the investigator.

³ Comments only provided for those patients who had an AE leading to death that was considered to be causally related to selumetinib by the investigator.

⁴ Novartis are the current trademark owners of RITALIN™.

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

CTCAE version 4.0.3, MedDRA version 21.0.

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AE Adverse event; BID Twice daily; CSR Clinical study report; CTCAE Common Terminology Criteria for Adverse Events; F Female; M Male; MedDRA Medical Dictionary for Regulatory Activities; NSCLC Non small cell lung cancer.

Source: Table 2.7.4.3.5.2.2 and Table 2.7.4.3.5.4.2 of the ISS Adult monotherapy pool, Module 5.3.5.3.

APPEARS THIS WAY ON ORIGINAL

The Applicant's Position:

No AEs with fatal outcome were reported in SPRINT Phase II Stratum 1 or SPRINT Phase I.

There were a number of deaths in the Adult monotherapy pool, but this is expected in a patient population with advanced cancer.

The FDA's Assessment:

The FDA generally agrees with the Applicant's analysis of deaths. In summary, there were no deaths in the pediatric pool at the time of the NDA submission and no pediatric deaths in the 90-day safety update report. Across the adult safety pool, 4% (14/347) of patients experienced death due to an AE or "other" reason. Three percent (10/347) had a fatal AE within 30 days of receiving selumetinib. These fatal AEs were pulmonary embolus (3), respiratory failure (2), cardiac arrest (1), meningeal metastases (1), death (1), acute kidney injury (1), and hemoptysis (1). The FDA analysis did not include one additional patient who experienced a fatal intestinal perforation because the CSR, as the Applicant has noted above, states that this patient died due to progressive disease (metastatic pancreatic cancer) rather than an AE. Three patients (0.9%) experienced a fatal AE that was at least possibly related to selumetinib: cardiac arrest, acute kidney injury, and respiratory failure. The FDA reviewed the narratives for patients (b) (6) and agrees with the Applicant's comments in Table 45. While selumetinib exposure cannot be ruled out as possibly contributing to these fatal AEs, there were multiple confounding variables in the causality analysis, including underlying disease and medical history.

The FDA additionally reviewed the narrative for patient (b) (6) with cause of death listed as "death". This patient was listed as having two Grade 5 AEs in the AE database: death and abdominal pain. The event of death was assessed as unrelated to selumetinib, but the event of abdominal pain was assessed as possibly related to selumetinib.

Patient (b) (6): 62 yo male with stage 4 melanoma with abdominal, bone, liver, lymph node, retroperitoneal and peripancreatic metastases, enrolled in Study D1532C00003. Significant medical history included myocardial infarction and placement of a cardiac stent. The patient had undergone resection of primary melanoma on left leg and radiation to the left inguinal and iliac lymph nodes. The patient experienced nausea and abdominal pain while on study requiring interruption. On Day 12, the patient had abdominal pain and abdominal distension. Both events were considered to be related to selumetinib by the investigator, and selumetinib was permanently discontinued due to the event of abdominal pain. A few days later, the patient experienced hematemesis at home but refused to seek medical attention. The patient died at home on Day 17. The death was reported by the emergency doctor; the cause of death was reported as unknown. There were no signs of tumor progression. There was no autopsy. The abdominal pain event was coded as Grade 5 due to the fatal outcome; however the event of unexplained death was considered unrelated to selumetinib.

Reviewer: *There is insufficient information in this case to determine selumetinib relatedness. The patient experienced GI toxicity and abdominal pain prior to the event, and both were considered related to study drug, and GI toxicity is a known drug class effect. The patient did not have evidence of progressive disease at the time of death. While the patient had extensive disease at enrollment including abdominal and peripancreatic metastases, selumetinib cannot be ruled out as possibly contributing to this fatal event.*

The FDA additionally reviewed the narrative for patient (b) (6) with cause of death listed as myocarditis and congestive heart failure. This death occurred outside of the 30-day reporting window, but the investigator assessed the event as relate to selumetinib.

Patient (b) (6): 37 yo with advanced melanoma. Medical history was significant for hypercholesterolemia, hypertension, renal transplantation and radiotherapy to the left axilla and supraclavicular fossa. The patient's concomitant medications included: clonidine, ezetimibe, pravastatin and sirolimus/prednisolone for approximately 3 years. Baseline LVEF was approximately 55%. On Day 6 of selumetinib, the patient had Grade 2 dermatitis acneiform leading to drug interruption. Selumetinib was never restarted. On Day 19, the patient experienced Grade 3 abdominal pain and received antibiotics for a possible infection. On Day 28 the patient was diagnosed with myocarditis and on Day 43, the patient developed congestive heart failure and died 5 days later. The myocarditis and congestive heart failure were assessed as related to selumetinib by the investigator. The investigator also thought that there may have been an interaction between selumetinib and sirolimus.

Reviewer: *There are multiple confounding variables that prevent a reliable assessment of causality in this case including the advanced underlying disease, long-term immunosuppression, concomitant medications and lack of details regarding the myocarditis diagnosis.*

Serious Adverse Events

Data:

Table 46 SPRINT Phase II Stratum 1 and the Pediatric Pool: SAEs by SOC and PT (Occurring in ≥2 Patients in Any Group) in SPRINT (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Patients with any SAE	12 (24.0)	14 (25.0)	2 (16.7)	2 (33.3)	1 (16.7)	17 (23.0)
Blood and lymphatic disorders	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Anaemia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Respiratory, thoracic and mediastinal disorders	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Hypoxia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Gastrointestinal disorders	3 (6.0)	4 (7.1)	0	1 (16.7)	0	4 (5.4)
Diarrhoea	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
General disorders and administration site conditions	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Pyrexia	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Investigations	2 (4.0)	3 (5.4)	0	1 (16.7)	0	3 (4.1)
Blood creatine phosphokinase increased	1 (2.0)	2 (3.6)	0	1 (16.7)	0	2 (2.7)

¹ Number (%) of patients with an SAE, sorted by SOC and then in decreasing frequency of events in the Phase II Stratum 1 treatment group

Patients with multiple SAEs are counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

AE Adverse event; BID Twice daily, CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities (version 21.0); PT Preferred term; SAE Serious adverse event; SOC System organ class.

Source: Table 2.7.4.3.3.1.1.1 of the ISS Pediatric monotherapy pool, Module 5.3.5.3

Table 47 Adult Monotherapy Pool: SAEs by SOC and PT (Occurring in ≥2% of Patients in Any Treatment Group) (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹		
	Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Total Selumetinib Adult Monotherapy Pool (N=347)
Patients with any SAE	26 (32.9)	65 (24.3)	91 (26.2)
Gastrointestinal disorders	9 (11.4)	15 (5.6)	24 (6.9)
Vomiting	4 (5.1)	4 (1.5)	8 (2.3)
Constipation	2 (2.5)	0	2 (0.6)
Infections and infestations	8 (10.1)	15 (5.6)	23 (6.6)
Lower respiratory tract infection	3 (3.8)	0	3 (0.9)
Blood and lymphatic system disorders	3 (3.8)	4 (1.5)	7 (2.0)
Anaemia	2 (2.5)	2 (0.7)	4 (1.2)
General disorders and administration site conditions	2 (2.5)	8 (3.0)	10 (2.9)
Pyrexia	2 (2.5)	2 (0.7)	4 (1.2)

¹ Number (%) of patients with an SAE, sorted in decreasing frequency of events in the hyd-sulfate treatment group. Patients with multiple SAEs were counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib. CTCAE version 4.0.3, MedDRA version 21.0.

AE Adverse event; BID Twice daily, CTCAE Common Terminology Criteria for Adverse Events; hyd-sulfate Hydrogen sulfate; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; SAE Serious adverse event; SOC System organ class.

Source: Table 2.7.4.3.3.1.2.1 of ISS Adult monotherapy pool, Module 5.3.5.3.

The Applicant's Position:

Serious Adverse Events: SPRINT Phase II Stratum 1 and the Pediatric Pool

Overall, 12 (24.0%) patients in SPRINT Phase II Stratum 1, and 17 (23.0%) patients in the Pediatric pool had at least 1 SAE during the treatment period (Table 46), and 8 (16.0%) patients in SPRINT Phase II Stratum 1 and 11 (14.9%) patients in the Pediatric pool, had AEs that led to hospitalisation. The incidence of SAEs considered to be possibly related to selumetinib were similar in SPRINT Phase II Stratum 1 (6 [12.0%]) and the Pediatric pool (8 [10.8%]) (Table 42).

The most commonly reported SAEs by PT in SPRINT Phase II Stratum 1, were anaemia, diarrhoea and hypoxia (2 [4.0%] patients, each), all other SAEs were reported in 1 (2.0%) patient, each. In the Pediatric pool, the most commonly reported SAEs by PT were anaemia, blood CPK increased, diarrhea, hypoxia, and pyrexia (2 [2.7%] patients each), all other SAEs were reported in 1 (1.4%) patient, each (Table 46).

Of the most frequently reported AEs by PT in SPRINT Phase II Stratum 1, only the PTs of blood CPK increased (2.0%), diarrhoea (4.0%), and pyrexia (2.0%), had SAEs reported.

In SPRINT Phase II Stratum 1, the majority of SAEs had recovered with either no action taken or following a temporary dose interruption or dose reduction at the DCO date for this analysis. The outcome was unknown for 1 (2.0%) patient with an SAE of humerus fracture, and 4 (8.0%) patients had an SAE that led to permanent discontinuation of selumetinib

The incidences of the most common SAEs in SPRINT Phase II Stratum 1 and the Pediatric pool were too low for a meaningful comparison with those observed in the Adult monotherapy pool (Table 46 and Table 47). Although the Pediatric pool and the Adult monotherapy pool has similar incidences of SAEs reported (23.0% and 26.2%, respectively), the incidence of SAEs in SPRINT Phase II Stratum 1 was lower than that of the adult hyd-sulfate sub-group (24.0% vs 39.2%, respectively).

Serious Adverse Events: Adult Monotherapy Pool

Overall, in the Adult monotherapy pool, 91 (26.2%) patients had at least 1 SAE (including fatal and non-fatal SAEs) during the treatment period, and SAEs were reported for 26 (39.2%) patients in the hyd-sulfate sub-group (Table 47). In total, 22 (27.8%) patients in the hyd-sulfate sub-group and 78 (22.5%) patients in the Adult monotherapy pool, had AEs that led to hospitalisation.

In the hyd-sulfate sub-group, the SAEs by PT reported in $\geq 2.0\%$ of patients were vomiting (4 [5.1%]), lower respiratory tract infection (3 [3.8%]), and anaemia, constipation and pyrexia (2 [2.5%] patients, each). In the Adult monotherapy pool, only the PT of vomiting (8 [2.3%]), was reported as an SAE in $\geq 2\%$ of patients (Table 47). With the exception of lower respiratory tract infection, all other SAEs reported in $\geq 2\%$ of patients are ADRs of selumetinib.

Whilst the most frequently reported AEs by PT in the hyd-sulfate sub-group and the Adult monotherapy pool were: fatigue, nausea, diarrhoea, dermatitis acneiform and oedema peripheral, the number of patients in whom these PTs were reported as SAEs was low: fatigue 0% vs 0%, nausea 1.3% vs 0.9%, diarrhoea 0 vs 0.9%, dermatitis acneiform 0% vs 0.3%, and oedema peripheral 0% vs 0.3%.

The incidence of SAEs considered to be possibly related to selumetinib were similar in the hyd-sulfate sub-group (7 [8.9%]) and the Adult monotherapy pool (32 [9.2%]).

In the Adult monotherapy pool, the majority (64.9%) of SAE events had recovered with either no action taken or following a temporary dose interruption or dose reduction, or were recovering. Selumetinib was permanently discontinued for 16 (4.6%) patients with non-fatal SAEs, and for 10 (2.9%) patients the SAEs were fatal.

The FDA's Assessment:

The FDA generally agrees with the Applicant's analysis of SAEs occurring during SPRINT and across the adult safety pool. In summary, among the 74 patients in the pediatric pool, 23% (17/74) experienced at least one SAE, including 11% who experienced a SAE considered at least possibly related to selumetinib. The events were varied; SAEs occurring in ≥ 2 patients included diarrhea, CPK elevation, anemia, pyrexia, and hypoxia. Across the adult safety cohort receiving the hyd-sulfate formulation, 33% (26/79) experienced at least one SAE including 10% with SAEs considered related to selumetinib. SAEs that occurred in ≥ 2 adult patients included vomiting (4), lower respiratory tract infection (3), anemia (2), constipation (2), and pyrexia (2). Please note that the absolute number of patients experiencing a SAE in the adult hyd-sulfate cohort (26) is correct; however, the "39.2%" result noted in paragraphs 5 and 6 of the Applicant's position statement appears to be a typographical error (32.9% is the correct SAE rate).

The FDA reviewed narratives for all SAEs occurring in the pediatric pool. Summaries of these narratives are presented here. The FDA was in agreement with the investigators' assessments in most cases and included reviewer comments following the summary when relevant.

SPRINT Phase II Stratum 1 SAEs

Patient (b) (6): CPK elevation

16 yo male with left truncal PN. Experienced asymptomatic Grade 2 CPK elevation starting on Day 25. AE became serious when severity increased to Grade 3 on Day 52. Remained Grade 3 and asymptomatic for 58 days, decreased to grade 2 for 56 days and then rose to **Grade 4** on Day 221. Dose was interrupted for 9 days followed by **dose reduction**. Cardiac workup showed CK-MB less than 5% and CPK elevation was considered to be a noncardiac event. Patient discontinued selumetinib on Day 585 for progressive disease. The investigator assessed the CPK elevation as related to selumetinib.

Patient (b) (6): Anemia, hypoxia, osteomyelitis, skin ulcer

11 yo male with head/neck PN and tracheostomy-dependent at enrollment due to airway compression. Medical history significant for respiratory failure due to infection and ventroperitoneal shunt for hydrocephalus. Skin ulcer SAE led to **permanent discontinuation** of selumetinib. On Day 540, patient was diagnosed with **Grade 4 skin ulcer** in region of previous pilonidal cyst. On Day 543 patient was seen by plastic surgery and orthopaedics and diagnosed with Stage 4 pressure ulcer and Grade 3 osteomyelitis. The patient underwent excision of coccyx bone. The patient had concurrent Grade 1 fever and Grade 3 anemia and received a blood transfusion. A Grade 4 hypoxia event occurred due to mucus plus on Day 544 and resolved with suctioning. The investigator assessed the events of skin ulcer, osteomyelitis and anemia as related to selumetinib and the hypoxia event as unrelated to selumetinib.

Patient (b) (6): **Bacterial tracheitis, hypoxia, constipation**

6 ½ yo male with target PN in head/neck region. Patient was tracheostomy-dependent at enrollment and had medical history significant for diarrhea, pulmonary stenosis and Pierre Robin syndrome. On Day 744, the patient experienced SAEs of Grade 2 bacterial tracheitis (positive MRSA culture) and Grade 3 hypoxia resulting in selumetinib interruption and hospitalization for antibiotics and oxygen support. The investigator considered these SAEs to be unrelated to selumetinib. On Day 778, the patient had Grade 2 constipation and was hospitalized for bowel clean-out. The patient had 7 prior constipation events on study. The investigator assessed the constipation as related to selumetinib and decreased bowel motility. The patient continued on selumetinib without dose modification during constipation.

Patient (b) (6): **Diarrhea**

3 ½ yo male with trunk and upper leg PN who presented on Day 291 with Grade 3 diarrhea requiring hospitalization. The patient had prior episodes of eosinophilic colitis and C. difficile colitis; however, C. difficile and stool cultures were negative at the time of this event. Selumetinib was interrupted for 2 days, and the diarrhea resolved in 8 days. The patient discontinued selumetinib on Day 564 (patient choice). The investigator assessed the diarrhea as related to selumetinib.

Patient (b) (6): **Acute kidney injury, anemia, blood creatinine increased, hyperkalemia, hyperuricemia, hypocalcemia, proteinuria**

11 yo male with PN of neck and trunk who presented on Day 196 with acute renal failure after more than two weeks of mild vomiting, diarrhea and poor oral intake. The patient was admitted with Grade 3 acute kidney injury, Grade 3 anemia, Grade 4 creatinine elevation, Grade 3 hyperkalemia, Grade 3 hypocalcemia and Grade 1 proteinuria. On Day 198, the patient developed Grade 4 hyperuricemia. All events resolved. The patient had interrupted selumetinib on Day 190, and these events led to **permanent discontinuation** of selumetinib. The investigator attributed the acute kidney injury, anemia, hyperkalemia, hyperuricemia, hypocalcemia, and proteinuria to selumetinib and the creatinine elevation to kidney injury.

Reviewer: This patient's kidney injury and electrolyte abnormalities could be partially attributed to dehydration given the prior weeks of vomiting and diarrhea. The selumetinib contribution may have been direct or indirect if selumetinib caused the GI toxicity preventing the patient from maintaining adequate hydration prior to the event.

Patient (b) (6): **Diarrhea**

15 ½ yo male with PN in neck/trunk region. The patient had two Grade 3 SAEs of diarrhea. Selumetinib was interrupted and restarted at a reduced dose after the first event on Day 18 and **permanently discontinued** on Day 64 after the second event of Grade 3 diarrhea.

Patient (b) (6): Hypotension

15 ½ yo with neck/trunk PN experienced **Grade 4** hypotension following a tumor debulking surgery. The investigator considered the hypotension to be unrelated to selumetinib and probably related to anesthesia. Other concurrent relevant adverse events reported at the time of the hypotension included sinus tachycardia and ejection fraction decreased.

Patient (b) (6): Colitis

6 yo male with left head PN experienced **Grade 3** colitis starting on Day 270 resulting in selumetinib interruption. The colitis was due to a C. difficile infection. The patient resumed selumetinib upon resolution.

Patient (b) (6): Influenza, pyrexia

15 ½ yo male with neck/trunk PN experienced **Grade 3** influenza on Day 386. Patient had Grade 2 pyrexia for two days concurrent with influenza. Patient required hospitalization. The investigator assessed the events of influenza and pyrexia as unrelated to selumetinib. The patient resumed selumetinib upon resolution.

Patient (b) (6): Hematoma, fracture, skin infection

10 yo male with trunk/extremity PN presented on Day 742 with **Grade 3** hematoma, fracture, and skin infection in the left arm. Medical history was significant for lymphedema in this arm, no sensation, and a recent fall. The patient was hospitalized for the infection and received IV antibiotics. Orthopedics managed the fracture. The investigator assessed the events of hematoma, skin infection and humerus fracture as unrelated to selumetinib.

Patient (b) (6): MPNST

15 yo male with neck/trunk PN experienced malignant transformation of PN to MPNST after one year on selumetinib. The left cervical MPNST was identified during pre-Cycle 13 MRI evaluation. The event resulted in selumetinib **discontinuation**, but the MPNST was not considered related to selumetinib exposure.

Patient (b) (6): Urinary tract infection (UTI), lymphopenia, neutropenia

4 yo male with trunk/extremity/pelvis PN and associated bladder dysfunction experienced two **Grade 3** UTIs during selumetinib treatment, both associated with Grade 3 lymphopenia and the first event associated with Grade 3 neutropenia. PMH significant for nephrostomy tubes and UTIs. The investigator assessed these events as unrelated to selumetinib.

There was one additional SAE that occurred in Patient (b) (6) from SPRINT Phase II Stratum 1 reported in the 90-day safety update. The patient was diagnosed with MPNST more than three years after initiation of selumetinib. Malignant transformation of PN to MPNST is a known risk in patients with NF1 PN and would not be considered related to selumetinib.

SPRINT Phase 1 SAEs

Patient (b) (6): **CPK elevation**

5 yo female with left pelvic PN who presented with asymptomatic **Grade 4** CPK increase on Day 505 resulting in selumetinib interruption and subsequent **dose reduction**. The patient had experienced intermittent Grade 1-2 CPK increases during the study and then a recurrent Grade 3 CPK increase on Day 1098. The patients experienced Grade 1 noncardiac chest pain concurrent with the second Grade 3 CPK increase. These latter events were ongoing at DCO.

***Reviewer:** The CSR states that there were no concurrent myalgia or muscle weakness symptoms during the CPK elevation events; however, the concurrent noncardiac chest pain is not well-described, and there is insufficient information to conclude that this pain was not musculoskeletal in origin.*

Patient (b) (6): **Pyrexia, vulval cellulitis**

8 yo female with left neck/chest PN presented with Grade 2 fever and **Grade 3** vulval cellulitis on Day 14. The patient was hospitalized for IV antibiotics, and selumetinib was held. The patient resumed selumetinib at a reduced dose upon resolution. This SAE was counted as a DLT at the 20mg/m² BID dose level during SPRINT Phase 1. The investigator assessed these events as related to selumetinib.

Patient (b) (6): **Fracture**

9 yo male with pelvis PN experienced a **Grade 3** fracture of right toe Day 139. Selumetinib was interrupted, but the investigator assessed the event as unrelated to study drug.

Patient (b) (6): **Headache**

6 yo male with left retroperitoneal PN presented with **Grade 3** headache on Day 968. Resolved in 2 days. Medical history significant for prior, less severe, headaches. Investigator assessed headache as unrelated to selumetinib.

Patient (b) (6): **Vomiting, abdominal pain, dehydration**

3 yo male with left eye PN, presented with **Grade 3** vomiting followed 2 days later by grade 3 abdominal pain and dehydration requiring hospitalization and selumetinib **interruption**. The investigator assessed these events as unrelated to selumetinib exposure.

SAEs - Pediatric Supportive Data

The FDA reviewed the SAE datasets for the selumetinib expanded access program in NF1 PN and externally-sponsored pediatric studies of selumetinib (SAEs were only reported from ongoing Study D1532C00043/PBTC-029 in pediatric patients with low grade glioma). As discussed in Section 8.2.1, calculation of AE incidence rates from these data is not possible due to an unreliable denominator. AEs that were considered serious and related to selumetinib and occurred in at least 2 patients with NF1 PN in the expanded access program include stomatitis, rash, paronychia, edema, hypertension, ejection fraction decrease, diarrhea, dermatitis

acneiform, CPK elevation, AST elevation and abdominal pain. Of these, SAEs that led to discontinuation of selumetinib were LVEF decrease and rash. Across the externally-sponsored pediatric studies of selumetinib, SAEs that were assessed as related to selumetinib and occurred in at least 2 patients included CPK increase, rash, paronychia, stomatitis, vision impairment, optic nerve disorder, vomiting, , dehydration, headache, and ALT elevation. Of these, SAEs that led to discontinuation of selumetinb were optic nerve disorder in 2 patients, vision impairment with retinal detachment in one patient, stomatitis, ALT elevation and rash.

Reviewer: *The SAEs that were reported in these supportive pediatric datasets are consistent with the safety profile of selumetinib and the MEK inhibitor drug class. Additional details on the ocular SAEs are provided in Section 8.2.5.*

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Table 48 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events Leading to Discontinuation of Selumetinib, by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Patients with any AE leading to discontinuation ²	6 (12.0)	6 (10.7)	1 (8.3)	0	2 (33.3)	9 (12.2)
Investigations	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Blood creatinine increased	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Weight increased	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Gastrointestinal disorders	1 (2.0)	1 (1.8)	1 (8.3)	0	1 (16.7)	3 (4.1)
Diarrhoea	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Gastro-oesophageal reflux disease	0	0	1 (8.3)	0	0	1 (1.4)
Nausea	0	0	1 (8.3)	0	0	1 (1.4)
Stomatitis	0	0	0	0	1 (16.7)	1 (1.4)
Infections and infestations	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Paronychia	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Peripheral nerve sheath tumour malignant	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Renal and urinary disorders	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Acute kidney injury	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Skin and subcutaneous tissue disorders	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)
Skin ulcer	1 (2.0)	1 (1.8)	0	0	0	1 (1.4)

Table 48 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events Leading to Discontinuation of Selumetinib, by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
General disorders and administration site conditions	0	0	0	0	1 (16.7)	1 (1.4)
Fatigue	0	0	0	0	1 (16.7)	1 (1.4)
Musculoskeletal and connective tissue disorders	0	0	0	0	1 (16.7)	1 (1.4)
Myalgia	0	0	0	0	1 (16.7)	1 (1.4)

¹ Number (%) of patients with an AE leading to discontinuation, sorted in decreasing frequency of events in Phase II Stratum 1.

² Action taken, selumetinib permanently stopped.

Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

MedDRA version 21.0.

AE Adverse event; BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities;

PT Preferred term; SOC System organ class.

Source: Table 2.7.4.3.6.1.1 of the ISS Pediatric monotherapy pool, Module 5.3.5.3.

Table 49 Adult Monotherapy Pool: Adverse Events Leading to Discontinuation of Selumetinib (Occurring in ≥2% of Patients in Any Treatment Group), by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹		
	Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Total Selumetinib Adult Monotherapy Pool (N=347)
Patients with any AE leading to discontinuation ²	23 (29.1)	31 (11.6)	54 (15.6)
General disorders and administration site conditions	6 (7.6)	3 (1.1)	9 (2.6)
Fatigue	4 (5.1)	0	4 (1.2)
Respiratory, thoracic and mediastinal disorders	5 (6.3)	5 (1.9)	10 (2.9)
Dyspnoea exertional	2 (2.5)	0	2 (0.6)
Investigations	4 (5.1)	0	4 (1.2)
Aspartate aminotransferase increased	2 (2.5)	0	2 (0.6)
Cardiac disorders	3 (3.8)	4 (1.5)	7 (2.0)
Left ventricular dysfunction	2 (2.5)	1 (0.4)	3 (0.9)

¹ Number (%) of patients with an AE leading to discontinuation, sorted in decreasing frequency of events in the selumetinib 75 mg BID treatment group

² Action taken, selumetinib permanently stopped

Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

CTCAE version 4.0.3, MedDRA version 21.0

AE Adverse event; BID Twice daily, CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; SOC System organ class.

Source: Table 2.7.4.3.6.1.2 of the ISS Adult monotherapy pool, Module 5.3.5.3.

The Applicant's Position:

Seven DAEs of selumetinib were reported for 6 (12.0%) patients of SPRINT Phase II Stratum 1. No AEs leading to permanent discontinuation of selumetinib were reported by more than 1 patient. Most DAEs were considered to be related to selumetinib by the investigator, except for AEs of blood creatinine increased (2 events in 1 patient) and malignant peripheral nerve sheath tumour. The percentage of patients with DAEs was low and all DAEs resolved after selumetinib was stopped. Similar observations and frequencies of DAEs were observed in the Pediatric pool (12 DAEs in 9 patients, 12.2%). Overall 5 DAE events were considered SAEs: skin ulcer, malignant peripheral nerve sheath tumour, acute kidney injury (1 event), creatinine increased (2 events in 1 patient), and diarrhoea.

The frequently observed AEs (>40%) that characterize the selumetinib safety profile (acneiform rashes, gastrointestinal events [diarrhoea and vomiting], paronychia and pyrexia) did not generally lead to discontinuation of selumetinib. The low percentage of permanent discontinuation of selumetinib due to AEs in SPRINT Phase II Stratum 1 and the Pediatric pool indicates that selumetinib at the recommended daily dose is tolerated by this pediatric NF1 patient population.

A similar overall incidence of DAEs was observed in the Adult monotherapy pool (15.6%) was similar, though the majority of DAEs were CTCAE Grade ≥ 3 and most DAEs were considered to be related to selumetinib by the investigator.

The FDA's Assessment:

The FDA agrees with the presentation of AEs leading to discontinuation of selumetinib as presented in Table 48 (SPRINT Phase II Stratum 1 and Pediatric pool columns) and Table 49. In summary, 12% (9/74) of patients in the pediatric pool experienced at least one AE that resulted in permanent discontinuation of selumetinib. These included diarrhea, paronychia, nausea, stomatitis, fatigue, acute kidney injury, skin ulcer, MPNST, increased weight, myalgia, and gastroesophageal reflux. None of these events occurred in more than one patient. All of the events, with the exception of MPNST and creatinine elevation (attributed to acute kidney injury which was considered possibly related to selumetinib), were assessed as at least possibly related to selumetinib exposure. Five events were considered SAEs: skin ulcer, MPNST, acute kidney injury, creatinine increased, and diarrhea.

Regarding the supportive adult data, AEs leading to selumetinib discontinuation occurred in 29% (23/79) of the adult hyd-sulfate cohort. Events that occurred in at least two patients included fatigue, dyspnea, AST elevation, and LV dysfunction. One patient experienced a retinal vein occlusion event that led to discontinuation. See Section 8.2.5.5 for a summary of this event.

The FDA reviewed narratives for all AEs leading to discontinuation of selumetinib in the pediatric pool. Discontinuation AEs that were serious are included in the SAE narrative summaries above. Summaries of the nonserious discontinuation AEs are presented below. The FDA was in agreement with the investigators' assessments and included reviewer comments following the summary when relevant.

SPRINT Phase II Stratum 1

Patient (b) (6): **Weight increased**

7 ½ yo with pelvis/extremity experienced **Grade 3** weight gain on Day 104 triggering selumetinib interruption and subsequent dose reduction. Recurrent Grade 3 weight increase on Day 203 led to interruption and a second dose reduction (from 10 mg QHS and 20 mg QAM to

10 mg BID). Study treatment was subsequently permanently discontinued on Day 277 due to weight gain. The investigator assessed the weight gain AE as possibly related to selumetinib. Upon later disease progression, the patient went on to restart selumetinib as part of the expanded access program.

Patient (b) (6): Paronychia

7 ½ yo with trunk/extremity PN who had multiple episodes of paronychia ranging in severity from Grade 1 to 3 while on selumetinib. The patient had 2 dose reductions and then permanently discontinued selumetinib on Day 449 after a recurrent **Grade 3** paronychia. The patient received multiple treatments for paronychia while on study including bacitracin, cefalexin, clindamycin, gentamicin, sulfamethoxazole/trimethoprim and triamcinolone. The investigator assessed the paronychia AEs as possibly related to selumetinib.

SPRINT Phase I

Patient (b) (6): Fatigue, myalgia, CPK increase

17 ½ yo male with neck/trunk/pelvis PN who had multiple events of CPK elevation during selumetinib exposure. He had 2 dose reductions for **Grade 3** CPK elevation. The patient reported Grade 1 myalgia during one CPK elevation which resolved without treatment and was considered related to selumetinib and to doing push-ups. The patient subsequently experienced **Grade 2 fatigue and myalgia** on Day 499 and selumetinib was discontinued on Day 500 based on these events. The patient had concurrent Grade 1 CPK increase starting Day 505. The myalgia resolved approximately 6 weeks later. The investigator assessed the myalgia and fatigue as possibly related to selumetinib.

***Reviewer:** Although the AE leading to discontinuation was coded as fatigue and myalgia, it is relevant that there was CPK elevation noted a few days after these symptoms manifested. This event appears to be a symptomatic CPK elevation.*

Patient (b) (6): Stomatitis

5 ½ yo female with left orbit PN started at dose level 30 mg/m² in SPRINT Phase 1. The patient had multiple episodes of stomatitis varying between Grade 1 and 3 in severity during selumetinib exposure. The patients had two dose reductions for stomatitis. A subsequent stomatitis on Day 997 led to interruption followed by discontinuation on Day 1007. The investigator assessed the stomatitis events as related to selumetinib.

Patient (b) (6): Gastroesophageal reflux disease

13 yo with neck/shoulder PN presented on Day 141 with Grade 2 GERD leading to discontinuation on Day 158. Assessed as related by the investigator.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Table 50 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events Leading to Dose Modification of Selumetinib (Occurring in ≥2% Patients in the Pediatric Pool), by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Patients with any AE leading to dose modification ²	40 (80.0)	45 (80.4)	8 (66.7)	5 (83.3)	5 (83.3)	58 (78.4)
Infections and infestations	20 (40.0)	23 (41.1)	5 (41.7)	3 (50.0)	3 (50.0)	31 (41.9)
Paronychia	7 (14.0)	8 (14.3)	2 (16.7)	1 (16.7)	2 (33.3)	12 (16.2)
Skin infection	4 (8.0)	4 (7.1)	0	0	0	4 (5.4)
Gastroenteritis	1 (2.0)	2 (3.6)	1 (8.3)	1 (16.7)	0	3 (4.1)
Pharyngitis streptococcal	2 (4.0)	2 (3.6)	0	0	1 (16.7)	3 (4.1)
Gastroenteritis viral	0	1 (1.8)	1 (8.3)	1 (16.7)	0	2 (2.7)
Upper respiratory tract infection	0	1 (1.8)	0	1 (16.7)	1 (16.7)	2 (2.7)
Urinary tract infection	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Viral infection	0	1 (1.8)	0	1 (16.7)	1 (16.7)	2 (2.7)
Gastrointestinal disorder	18 (36.0)	22 (39.3)	5 (41.7)	4 (66.7)	3 (50.0)	30 (40.5)
Vomiting	12 (24.0)	15 (26.8)	3 (25.0)	3 (50.0)	1 (16.7)	19 (25.7)
Diarrhoea	6 (12.0)	7 (12.5)	2 (16.7)	1 (16.7)	2 (33.3)	11 (14.9)
Abdominal pain upper	4 (8.0)	5 (8.9)	0	1 (16.7)	0	5 (6.8)
Nausea	5 (10.0)	5 (8.9)	2 (16.7)	0	1 (16.7)	8 (10.8)
Stomatitis	2 (4.0)	3 (5.4)	0	1 (16.7)	2 (33.3)	5 (6.8)
Dental caries	2 (4.0)	2 (3.6)	1 (8.3)	0	0	3 (4.1)
Abdominal discomfort	0	1 (1.8)	1 (8.3)	1 (16.7)	0	2 (2.7)
Abdominal pain	0	1 (1.8)	0	1 (16.7)	1 (16.7)	2 (2.7)

Table 50 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events Leading to Dose Modification of Selumetinib (Occurring in ≥2% Patients in the Pediatric Pool), by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
General disorders and administration site conditions	11 (22.0)	12 (21.4)	1 (8.3)	1 (16.7)	1 (16.7)	14 (18.9)
Influenza-like illness	7 (14.0)	8 (14.3)	1 (8.3)	1 (16.7)	0	9 (12.2)
Pyrexia	4 (8.0)	5 (8.9)	1 (8.3)	1 (16.7)	0	5 (6.8)
Injury, poisoning and procedural complications	6 (12.0)	7 (12.5)	1 (8.3)	1 (16.7)	1 (16.7)	9 (12.2)
Fracture	2 (4.0)	2 (3.6)	0	0	1 (16.7)	3 (4.1)
Investigations	5 (10.0)	6 (10.7)	1 (8.3)	1 (16.7)	3 (50.0)	10 (13.5)
Weight increased	3 (6.0)	3 (5.4)	0	0	0	3 (4.1)
Blood creatine phosphokinase increased	1 (2.0)	2 (3.6)	1 (8.3)	1 (16.7)	2 (33.3)	5 (6.8)
Skin and subcutaneous tissue disorders	4 (8.0)	6 (10.7)	3 (25.0)	2 (33.3)	1 (16.7)	10 (13.7)
Rash maculo-papular	1 (2.0)	3 (5.4)	1 (8.3)	2 (33.3)	0	4 (5.4)
Pruritus	1 (2.0)	2 (3.6)	0	1 (16.7)	0	2 (2.7)
Dermatitis acneiform	1 (2.0)	1 (1.8)	0	0	1 (16.7)	2 (2.7)
Dry skin	1 (2.0)	1 (1.8)	1 (8.3)	0	0	2 (2.7)
Respiratory, thoracic and mediastinal disorders	4 (8.0)	5 (8.9)	0	1 (16.7)	0	5 (6.8)
Hypoxia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Eye disorders	3 (6.0)	3 (5.4)	0	0	0	3 (4.1)
Vision blurred	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Nervous system disorders	2 (4.0)	3 (5.4)	1 (8.3)	1 (16.7)	0	4 (5.4)
Headache	2 (4.0)	3 (5.4)	1 (8.3)	1 (16.7)	0	4 (5.4)
Psychiatric disorders	3 (6.0)	3 (5.4)	0	0	0	3 (4.1)
Insomnia	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)

Table 50 SPRINT Phase II Stratum 1 and the Pediatric Pool: Adverse Events Leading to Dose Modification of Selumetinib (Occurring in ≥2% Patients in the Pediatric Pool), by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	Number (%) of Patients ¹					
	Phase II Stratum 1 25 mg/m ² BID (N=50)	Phase I + Phase II Stratum 1 25 mg/m ² BID (N=56)	Phase I 20 mg/m ² BID (N=12)	Phase I 25 mg/m ² BID (N=6)	Phase I 30 mg/m ² BID (N=6)	Pediatric Pool All Doses (N=74)
Renal and urinary disorders	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)
Haematuria	2 (4.0)	2 (3.6)	0	0	0	2 (2.7)

¹ Number (%) of patients with an AE leading to dose modification of selumetinib, sorted in decreasing frequency of events in the selumetinib 25mg/m² BID treatment group.

² AE action taken, dose increased, dose reduced or drug interrupted.

Patients with multiple AEs leading to dose modification are counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after (or with an onset date before, whose CTCAE grade worsened on or after) the date of first dose and up to and including 30 days following the date of last dose of selumetinib.

MedDRA version 21.0.

AE Adverse event; BID Twice daily; CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities;

PT Preferred term; SOC System organ class.

Source: Table 2.7.4.3.7.1.1 of the ISS Pediatric pool, Module 5.3.5.3.

Table 51 Adult Monotherapy Pool: Adverse Events Leading to Dose Modification of Selumetinib Occurring in ≥2% Patients in Any Treatment Group, by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA SOC and PT	N (%) of Patients ¹		
	Hyd-sulfate Sub-group 75 mg BID (N=79)	Free Base Sub-group 100 mg BID (N=268)	Total Selumetinib Adult Monotherapy Pool (N=347)
Patients with any AE leading to dose modification ²	19 (24.1)	83 (31.0)	102 (29.4)
Gastrointestinal disorders	6 (7.6)	27 (10.1)	33 (9.5)
Diarrhoea	2 (2.5)	7 (2.6)	9 (2.6)
Vomiting	2 (2.5)	5 (1.9)	7 (2.0)
Nausea	0	6 (2.2)	6 (1.7)
Skin and subcutaneous tissue disorders	5 (6.3)	37 (13.8)	42 (12.1)
Rash	2 (2.5)	0	2 (0.6)
Dermatitis acneiform	1 (1.3)	23 (8.6)	24 (6.9)
General disorders and administration site conditions	3 (3.8)	11 (4.1)	14 (4.0)
Pyrexia	2 (2.5)	3 (1.1)	5 (1.4)
Respiratory, thoracic and mediastinal disorders	3 (3.9)	5 (1.9)	8 (2.3)
Dyspnoea	2 (2.5)	1 (0.4)	3 (0.9)

¹ Number (%) of patients with an AE leading to dose modification, sorted in decreasing frequency of events in the selumetinib 75mg BID treatment group.

² AE action taken, dose increased, dose reduced or drug interrupted.

Patients with multiple AEs leading to dose modification are counted once for each SOC/PT.

Percentages are based on the total numbers of patients in the treatment group (N).

Includes AEs with an onset date on or after the date (or with an onset date before, whose CTCAE grade worsened on or after) of first dose and up to and including 30 days following the date of last dose of selumetinib.

CTCAE version 4.0.3, MedDRA version 21.0.

AE Adverse event; BID Twice daily, CTCAE Common Terminology Criteria for Adverse Events; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term; SOC System organ class.

Source: Table 2.7.4.3.7.1.2 of the ISS Adult monotherapy pool, Module 5.3.5.3.

The Applicant's Position:

The incidence of AEs leading to dose modification (interruption and/or reduction) was similar in SPRINT Phase II Stratum 1 and the Pediatric pool (80.0% vs 78.4%, respectively). All patients who had a dose modification had an AE leading to dose interruption in both SPRINT Phase II Stratum 1 (40 [80.0%]) and the Pediatric pool (58 [78.4%]). The incidence of AE leading to dose reduction of selumetinib was 24.0% (12 patients) in SPRINT Phase II Stratum 1 and 32.4% (24 patients) in the Pediatric pool.

The most common AEs leading to dose modification of selumetinib were all consistent with the known safety profile of selumetinib or commonly noted in any pediatric population (ie, influenza-like illness).

In SPRINT Phase II Stratum 1, the most commonly reported AEs leading to dose modification (interruption and/or reduction) of selumetinib were vomiting (12 [24.0%]), influenza-like illness and paronychia (7 [14.0%], each), diarrhoea (6 [12.0%]), and nausea (5 [10.0%]). All other AEs leading to modification of the selumetinib were reported in ≤ 4 (8.0%) patients. Similar observations and incidences of AEs were observed in the Pediatric pool. Overall, the incidence of AEs leading to dose modifications was higher in in the Pediatric pool compared to the Adult monotherapy pool (78.4% compared with 29.4%, respectively), however the higher incidence of AEs leading to dose modifications in the pediatric population is most likely due to the longer duration of exposure in SPRINT compared to the adult monotherapy studies.

The FDA's Assessment:

The FDA agrees with the Applicant's analysis of AEs leading to dose modifications (interruptions or reductions) of selumetinib in SPRINT Phase 2 Stratum 1 and across the pediatric pool as presented in Table 50 and across the adult safety pool as presented in Table 51.

Dose modifications for AEs occurred in nearly 80% of pediatric patients. The most common AEs leading to dose modifications in more than 10% of pediatric patients were vomiting, diarrhea, nausea, flu-like illnesses and paronychia. The majority of patients were able to resume dosing upon resolution of the AE without dose reduction.

Approximately 1/3 of patients in the pediatric pool required dose reduction due to an AE. AEs that required dose reduction in at least 2 patients were CPK elevation, increased weight, paronychia, stomatitis and rash. One patient required dose reduction for decreased ejection fraction.

Nearly 25% of patients in the adult pool receiving the hyd-sulfate formulation required dose modifications for AEs. Similar to the pediatric pool, gastrointestinal and skin toxicities most commonly led to dose interruptions. Five percent of patients in the adult hyd-sulfate cohort required dose reduction for AEs.

The FDA agrees that the increased incidence of dose interruptions and dose reductions in the pediatric pool as compared to the adult safety pool is due to the longer exposure time in pediatric patients. The FDA also acknowledges that some selumetinib interruptions in the pediatric population were due to common childhood illnesses that may not have been related to selumetinib exposure. Further, withholding drug for more mild-moderate toxicities may be more reasonable in a benign tumor population.

Treatment Emergent Adverse Events and Adverse Reactions

The FDA's Assessment:

The safety databases for SPRINT Phase II Stratum 1, the pediatric pool, and the adult monotherapy pool were analyzed at each level of the MedDRA hierarchy for treatment emergent AEs (TEAEs). The tables in this section summarize the incidence of TEAEs, defined as AEs that occurred from the time of the first dose up to 30 days after the last dose of selumetinib or data cutoff date if that date was earlier. Almost all pediatric patients (99%) and adult patients (98%) exposed to selumetinib had at least one AE during treatment.

The SPRINT data indicate that AEs were frequent and varied in the pediatric NF1 PN population. Table 52 represents the most frequently affected systems (> 20% incidence) at the system organ class (SOC) level. Note that during SPRINT, laboratory values outside of normal range were reported as AEs regardless of clinical significance; therefore, nearly all patients experienced an AE falling under the Investigations category.

Table 52 SPRINT AEs by SOC ($\geq$ 20% Incidence)

System Organ Class	SPRINT Phase II N=50 n (%)	Pediatric Pool N=74 n (%)
Investigations	49 (98)	73 (99)
Skin and subcutaneous tissue disorders	49 (98)	73 (99)
Gastrointestinal disorders	48 (96)	72 (97)
Metabolism and nutrition disorders	48 (96)	72 (97)
General disorders and administration site conditions	42 (84)	65 (88)
Infections and infestations	41 (82)	62 (84)
Respiratory, thoracic and mediastinal disorders	41 (82)	62 (84)
Musculoskeletal and connective tissue disorders	35 (70)	55 (74)
Nervous system disorders	35 (70)	53 (72)
Renal and urinary disorders	25 (50)	40 (54)
Blood and lymphatic system disorders	23 (46)	35 (47)
Injury, poisoning and procedural complications	22 (44)	37 (50)
Psychiatric disorders	20 (40)	29 (39)
Eye disorders	17 (34)	24 (32)
Vascular disorders	14 (28)	21 (28)
Cardiac disorders	12 (24)	23 (31)
Ear and labyrinth disorders	9 (18)	15 (20)

Source: ISS Pediatric pool ADAE.xpt

At the PT level, excluding laboratory abnormalities, AEs that occurred in $\geq 30\%$ of pediatric patients in SPRINT Phase II Stratum 1 included vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, dermatitis acneiform, stomatitis, headache, oropharyngeal pain, paronychia, pruritus, cough, dermatitis, constipation, nasal congestion, hair disorder, influenza like illness, and allergic rhinitis. Grade 3-4 AEs that occurred in at least 5% of patients included vomiting, rash, CPK elevation, diarrhea, pyrexia and paronychia. Table 53 summarizes common TEAEs ($\geq 20\%$), excluding laboratory abnormalities, from SPRINT Phase II Stratum 1 and the pediatric pool.

Table 53 Common TEAEs ($\geq 20\%$) in SPRINT

Preferred Term	SPRINT Phase II N=50		Pediatric Pool N=74	
	Any Grade (%)	Grade $\geq 3^*$ (%)	Any Grade (%)	Grade $\geq 3^*$ (%)
Any AE	49 (98)	31 (62)	73 (99)	50 (68)
Vomiting	41 (82)	3 (6)	61 (82)	6 (8)
Rash ¹	46 (80)	3 (6)	67 (91)	6 (8)
Abdominal pain ²	38 (76)	0	58 (78)	1 (1)
Diarrhea	35 (70)	8 (16)	57 (77)	11 (15)
Nausea	33 (66)	1 (2)	54 (73)	1 (1)
Dry skin	30 (60)	0	43 (58)	0
Musculoskeletal pain ³	29 (58)	0	47 (64)	0
Fatigue ⁴	28 (56)	0	45 (61)	0
Pyrexia	28 (56)	4 (8)	42 (57)	6 (8)
Dermatitis acneiform	25 (50)	2 (4)	40 (54)	2 (3)
Stomatitis ⁵	25 (50)	0	38 (51)	1 (1)
Headache	24 (48)	1 (2)	40 (54)	2 (3)
Oropharyngeal pain	24 (48)	0	30 (41)	0
Paronychia ⁶	24 (48)	3 (6)	35 (47)	7 (10)
Pruritus	23 (46)	0	31 (42)	0
Cough	20 (40)	0	37 (50)	0
Dermatitis ⁷	18 (36)	2 (4)	25 (34)	2(3)
Constipation	17 (34)	0	25 (34)	0
Nasal congestion	17 (34)	0	32 (43)	0
Hair disorder ⁸	16 (32)	0	29 (39)	0

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Preferred Term	SPRINT Phase II N=50		Pediatric Pool N=74	
	Any Grade (%)	Grade $\geq$ 3* (%)	Any Grade (%)	Grade $\geq$ 3* (%)
Influenza like illness ⁹	15 (30)	2 (4)	21 (28)	2 (3)
Rhinitis allergic	15 (30)	0	16 (22)	0
Dizziness	14 (28)	0	18 (24)	0
Epistaxis	14 (28)	0	22 (30)	0
Otitis media	14 (28)	0	22 (30)	0
Fall	13 (26)	0	18 (24)	0
Pharyngitis ¹⁰	12 (24)	0	16 (22)	0
Decreased appetite	11 (22)	0	16 (22)	0 (0)
Ejection fraction decreased	11 (22)	0	17 (23)	1 (1)
Hematuria	11 (22)	1 (2)	18 (24)	1 (1)
Pain	11 (22)	0	12 (16)	0
Proteinuria	11 (22)	0	17 (23)	0
Edema ¹¹	10 (20)	0	15 (20)	0
Insomnia	10 (20)	1 (2)	15 (20)	1 (1)
Sinus tachycardia	10 (20)	0	19 (26)	0
Skin infection ¹²	10 (20)	1 (2)	16 (22)	2 (3)
Upper respiratory tract infection	8 (16)	0	16 (22)	0
Gastroenteritis ¹³	7 (14)	0	17 (23)	5 (7)

Source: ISS Pediatric pool ADAE.xpt

*No Grade 5 TEAEs.

¹ Rash (all) includes dermatitis acneiform; rash maculo-papular; erythema; rash pustular; rash; urticaria; exfoliative rash; rash pruritic; rash erythematous

² Abdominal pain includes abdominal pain; abdominal pain upper, abdominal discomfort, gastrointestinal pain

³ Musculoskeletal pain includes pain in extremity; back pain; neck pain; musculoskeletal pain

⁴ Fatigue includes fatigue, malaise

⁵ Stomatitis includes stomatitis; mouth ulceration

⁶ Paronychia includes paronychia, nail infection

⁷ Dermatitis includes dermatitis; dermatitis atopic; dermatitis diaper; eczema; seborrheic dermatitis; skin irritation dermatitis bullous; dermatitis contact

⁸ Hair disorder includes alopecia, hair color change, hair disorder

⁹ Influenza includes influenza, influenza like illness

¹⁰ Pharyngitis includes pharyngitis streptococcal, pharyngitis

¹¹ Edema includes peripheral swelling, peripheral edema, localized edema

¹² Skin infection includes skin infection; abscess; cellulitis; impetigo; staphylococcal skin infection

¹³ Gastroenteritis includes gastroenteritis, gastroenteritis salmonella, gastroenteritis viral, viral diarrhea

The FDA’s analysis of the adult safety data demonstrated that AEs were less frequent and less varied in adult patients with cancer receiving selumetinib as compared to pediatric patients with NF1 PN. As previously discussed, this apparent difference is mostly due to the relatively short selumetinib exposure time for adults (median of 1.6 months for hyd-sulfate cohort) as compared to pediatric patients (median of 25.6 months for pediatric pool) in addition to inherent differences in the study populations.

Table 54 provides a side by side presentation of common AEs ($\geq 20\%$) occurring in the pediatric pool and the adult hyd-sulfate pool. Almost all AEs occurred more frequently in the pediatric pool. Excluding laboratory abnormalities, AEs occurring in pediatric patients with a ≥ 2 -fold incidence compared with the incidence in adult patients were: vomiting, abdominal pain, musculoskeletal pain, dry skin, pyrexia, headache, stomatitis, cough, paronychia, nasal congestion, pruritis, sore throat, hair disorders, dermatitis, otitis media, influenza-like illness, upper respiratory infection (URI), epistaxis, EF decrease, gastroenteritis, rhinitis, skin infection, pharyngitis, insomnia, pain and dehydration. It is expected that many AEs (e.g., vomiting, diarrhea, abdominal pain, fever, headache, URI, nasal congestion, paronychia, stomatitis, sore throat, dermatitis, ear infection, gastroenteritis, pharyngitis) would be more prevalent in a pediatric study population.

Table 54 Common TEAEs ($\geq 20\%$) Pediatric and Adult Pools

Preferred Term	Pediatric Pool N=74		Adult Pool N=79	
	Any Grade (%)	Grade $\geq 3^*$ (%)	Any Grade (%)	Grade $\geq 3^*$ (%)
Any AE	73 (99)	50 (68)	77 (98)	47 (60)
Rash ¹	67 (91)	6 (8)	53 (67)	7 (8)
Vomiting	61 (82)	6 (8)	17 (22)	3 (4)
Abdominal pain ²	58 (78)	1 (1)	22 (28)	2 (3)
Diarrhea	57 (77)	11 (15)	36 (46)	0 (0)
Nausea	54 (73)	1 (1)	38 (48)	1 (1)
Musculoskeletal pain ³	47 (64)	0	10 (13)	0
Fatigue ⁴	45 (61)	0 (0)	40 (51)	7 (9)
Dry skin	43 (58)	0 (0)	16 (20)	0 (0)
Pyrexia	42 (57)	6 (8)	9 (11)	2 (3)
Dermatitis acneiform	40 (54)	2 (3)	27 (34)	2 (3)
Headache	40 (54)	2 (3)	12 (15)	0 (0)
Stomatitis ⁵	38 (51)	1 (1)	7 (9)	0 (0)
Cough	37 (50)	0 (0)	18 (23)	0 (0)

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Preferred Term	Pediatric Pool N=74		Adult Pool N=79	
	Any Grade (%)	Grade $\geq$ 3* (%)	Any Grade (%)	Grade $\geq$ 3* (%)
Paronychia ⁶	35 (47)	7 (10)	1 (1)	0 (0)
Nasal congestion	32 (43)	0 (0)	0 (0)	0 (0)
Pruritus	31 (42)	0 (0)	9 (11)	0 (0)
Oropharyngeal pain	30 (41)	0 (0)	6 (8)	0 (0)
Hair disorder ⁷	29 (39)	0 (0)	5 (6)	0 (0)
Constipation	25 (34)	0 (0)	20 (25)	2 (3)
Dermatitis ⁸	25 (34)	2(3)	2 (3)	0 (0)
Hyperglycaemia	23 (31)	0 (0)	1 (1)	0 (0)
Epistaxis	22 (30)	0 (0)	5 (6)	0 (0)
Otitis media	22 (30)	0 (0)	0 (0)	0 (0)
Influenza-like illness ⁹	21 (28)	2 (3)	4 (5)	0 (0)
Sinus tachycardia	19 (26)	0 (0)	0 (0)	0 (0)
Dizziness	18 (24)	0 (0)	15 (19)	0 (0)
Fall	18 (24)	0 (0)	0 (0)	0 (0)
Hematuria	18 (24)	1 (1)	2 (3)	0 (0)
Ejection fraction decreased	17 (23)	1 (1)	2 (3)	0 (0)
Proteinuria	17 (23)	0 (0)	0 (0)	0 (0)
Gastroenteritis ¹⁰	17 (23)	5 (7)	1 (1)	0 (0)
Decreased appetite	16 (22)	0 (0)	19 (24)	0 (0)
Rhinitis allergic	16 (22)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	16 (22)	0 (0)	2 (3)	0 (0)
Skin infection ¹¹	16 (22)	2 (3)	1 (1)	0 (0)
Pharyngitis ¹²	16 (22)	0 (0)	0 (0)	0 (0)
Insomnia	15 (20)	1 (1)	5 (6)	0 (0)
Edema ¹³	15 (20)	0 (0)	25 (32)	1 (1)

Source: ISS Pediatric pool ADAE.xpt; ISS Adult monotherapy pool ADAE.xpt

*No Grade 5 TEAS.

¹ Rash (all) includes dermatitis acneiform; rash; rash maculo-papular; skin rash; erythema; exfoliative rash; rash pruritic; rash erythematous; rash pustular; rash generalized; palmar-plantar erythrodysesthesia syndrome; urticaria

² Abdominal pain includes abdominal pain; abdominal pain upper, abdominal discomfort, gastrointestinal pain

³ Musculoskeletal pain includes pain in extremity; back pain; neck pain; musculoskeletal pain

⁴ Fatigue includes fatigue, malaise

⁵ Stomatitis includes stomatitis; mouth ulceration

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- ⁶ Paronychia includes paronychia, nail infection
- ⁷ Hair disorder includes alopecia, hair color change, hair disorder
- ⁸ Dermatitis includes dermatitis; dermatitis atopic; dermatitis diaper; eczema; seborrheic dermatitis; skin irritation dermatitis bullous; dermatitis contact
- ⁹ Influenza includes influenza, influenza like illness
- ¹⁰ Gastroenteritis includes gastroenteritis, gastroenteritis salmonella, gastroenteritis viral, viral diarrhea
- ¹¹ Skin infection includes skin infection; abscess; cellulitis; impetigo; staphylococcal skin infection
- ¹² Pharyngitis includes pharyngitis streptococcal, pharyngitis
- ¹³ Edema includes peripheral swelling, peripheral edema, localized edema

The Applicant's analysis of longer term safety data submitted with the 90-day safety update did not detect new safety signals, and the frequency and severity of common AEs in pediatric patients were similar in the cumulative analysis when compared to the results submitted with the original NDA.

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Laboratory Findings

The FDA's Assessment:

Laboratory tests to assess hematology parameters, liver function (alkaline phosphatase, ALT, AST, bilirubin), chemistries (sodium, potassium, chloride, BUN, creatinine, glucose), minerals (magnesium, phosphorus, calcium), amylase, lipase, and CPK were measured at baseline and prior to each 28 day cycle for the first 5 cycles and then every other cycle thereafter during SPRINT. Table summarizes the common laboratory abnormalities for patients with NF1 PN receiving selumetinib during SPRINT. Incidence rates may differ from the laboratory abnormalities observed in the AE dataset because the denominator used to calculate the rate is based on the number of patients with a baseline value and at least one post-treatment value for that parameter rather than the safety population. Grade 3 or 4 chemistry abnormalities were uncommon; those that occurred in 2 or more of patients included anemia, neutropenia, hyperkalemia and increases in ALT, CPK and lipase.

Liver enzyme elevation was common but usually low grade during SPRINT. No patients in the pediatric pool had elevations of either ALT or AST preceding or concurrent with elevations in total bilirubin. In the adult supportive data, 7 patients with metastatic uveal melanoma in Study D1344C00001 (N=129; selumetinib or placebo in combination with dacarbazine) had concurrent elevation of liver enzymes and bilirubin. All patients had liver metastases and concurrent elevations in alkaline phosphatase; therefore, these events did not meet Hy's Law criteria.

CPK elevation was common during SPRINT. CPK elevation was not common in the adult data because CPK was not routinely assessed in early studies of selumetinib. CPK elevation and rhabdomyolysis are safety signals associated with the MEK inhibitor drug class. See Section 8.2.5.4 for a more detailed discussion of CPK elevation.

Table 55 Laboratory Abnormalities, SPRINT

Lab Assessment	SPRINT Phase 2		Pediatric Pool	
	Any Grade (%)	Grade $\geq$ 3* (%)	Any Grade (%)	Grade $\geq$ 3* (%)
Hematology				
Anemia	20 (41)	2 (4)	14 (19)	1 (1)
Lymphopenia	11 (22)	1 (2)	20 (27)	1 (1)
Neutropenia	16 (33)	2 (4)	26 (36)	3 (4)
Thrombocytopenia	6 (12)	0	8 (11)	0
Chemistry				
Increased CPK	33 (79)	2 (5)	51 (77)	7 (11)
Hypoalbuminemia	25 (51)	0	31 (42)	0

Lab Assessment	SPRINT Phase 2		Pediatric Pool	
	Any Grade (%)	Grade $\geq$ 3* (%)	Any Grade (%)	Grade $\geq$ 3* (%)
Increased AST	21 (43)	1 (2)	33 (46)	1 (1)
Increased ALT	17 (35)	2 (4)	26 (36)	2 (3)
Increased lipase	14 (34)	2 (5)	NA	NA
Hyperkalemia	13 (27)	2 (4)	15 (21)	3 (4)
Hypokalemia	9 (18)	1 (2)	8 (11)	1 (1)
Hyponatremia	9 (18)	0	12 (16)	0
Hyponatremia	8 (16)	0	7 (10)	0
Increased creatinine	7 (14)	1 (2)	27 (37)	1 (1)
Hypomagnesemia	5(10)	0	11 (15)	0
Increased amylase	4 (10)	0	NA	NA
Increased bilirubin	1 (2)	0	5 (7)	0

Source: ISS Pediatric Pool ADLB.xpt; NA: Lipase and amylase parameters not included in pooled data

* No Grade 5 laboratory abnormalities.

Vital Signs

Data:

Not applicable.

The Applicant's Position:

There were no unexpected changes noted in vital signs, ophthalmic or physical examination safety parameters in patients treated with selumetinib in the pediatric or the Adult monotherapy pool populations, and no individual abnormalities raised any safety concerns. Diastolic and systolic BP did not change appreciably during the study, with mean and median values over time remaining consistent.

The FDA's Assessment:

The Applicant's general statement that there were no unexpected changes in vital signs, ophthalmic or physical examination assessments in pediatric and adult patients treated with selumetinib is vague and potentially misleading. Ophthalmic assessments are discussed in Section 8.2.5.5.

Vital signs were collected once per cycle for the first 5 cycles and as clinically indicated during SPRINT. The CSRs for SPRINT indicate that vital sign changes were generally not a safety concern. Among the 74 patients in the pediatric pool, 16% (12/74) experience Grade 1-2 hypertension during selumetinib exposure. Hypertension AEs were not serious and did not

result in dose modification. Tachycardia or bradycardia occurred in 30% of patients and all AEs were Grade 1 except for two Grade 2 tachycardia AEs.

Electrocardiograms (ECGs)

Data:

Not applicable.

The Applicant's Position:

There were no clinically relevant trends observed for ECG parameters in the pediatric and adult populations.

The FDA's Assessment:

ECGs were performed at baseline and as clinically indicated during SPRINT. The FDA agrees with the Applicant's assessment that there were no clinically relevant ECG patterns observed in the pediatric pool. The FDA did not review the ECG data for the adult safety pool.

QT

Data:

Assessment of QTc in healthy subjects concluded a single oral dose of selumetinib 75 mg was not associated with any incidence of QTcF intervals greater than 450 msec or increases from baseline of greater than 30 msec. No effect on ECG variables was considered clinically significant and is in agreement with what has been observed in patient studies.

The Applicant's Position:

Selumetinib does not prolong the QTc interval in healthy adult subjects and does not have any adverse effect on cardiac repolarization.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Immunogenicity

Data:

Not applicable.

The Applicant's Position:

In SPRINT Phase II Stratum I data, the Pediatric pool and Adult monotherapy pool, there are no events suggestive immunogenicity or allergy to selumetinib (such as AEs of severe hypersensitivity).

The FDA's Assessment:

The FDA agrees that immunogenicity is not a safety concern for selumetinib.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Paronychia

Data:

See the Applicant's Position below.

The Applicant's Position:

Nail disorders have been identified as an adverse event of special interest (AESI) with selumetinib treatment. In general, reported events of nail disorders were non-serious, mild or moderate in severity, did not lead to treatment discontinuation, and generally resolved during continued treatment with selumetinib.

Within the grouped term of nail disorder events, all 23 AEs reported in SPRINT Phase II Stratum 1 were AEs of paronychia. AEs of paronychia were predominantly CTCAE Grade 1 or Grade 2; 3 (6.0%) patients had AEs of CTCAE Grade 3. The median time to onset was 306.0 days and the median duration was 96.0 days. Seven patients had a selumetinib dose interruption, 3 patients had a selumetinib dose reduction, and 1 patient experienced an AE of paronychia which led to permanent discontinuation of selumetinib. In SPRINT Phase II Stratum 1, all of the AEs of paronychia were reported as resolved at the DCO.

The majority of the pediatric patients responded to dose modification and additional symptomatic/supportive treatment. At the time of DCO, ongoing events were either mild or moderate in severity. This observation can be attributed to the fact that inhibition of the mitogen activated protein kinase pathway results in growth arrest and premature differentiation of keratinocytes (Roberts and Der 2007). In addition, pediatric patients are more prone to acute paronychia through direct inoculation of fingers with flora from the mouth secondary to finger sucking and nail biting (Rockwell 2001).

The FDA's Assessment:

The FDA agrees with the Applicant's analysis of paronychia in SPRINT Phase II, Stratum 1.

Paronychia is a toxicity that has been associated with a number of targeted agents including EGFR inhibitors and MEK inhibitors. The underlying mechanism of skin and nail toxicities associated with use of these agents may be via modifications of signals through the RAS/RAF/MEK/ ERK pathway, affecting proliferation and differentiation of epidermis cells.

Paronychia (FDA grouped PTs: paronychia and nail infection) was a common AE and occurred in 47% (35/74) of patients in the pediatric pool including 10% (7/74) of patients who experienced Grade 3 paronychia. Four patients required dose reductions for paronychia including one patient who was dose-reduced twice prior to permanently discontinuing selumetinib for paronychia. Except for 11 patients with unknown outcomes, the rest of the patients with paronychia recovered with symptomatic treatment and supportive care.

Whereas most other common AEs in the pediatric pool occurred at increased incidence rates in the first year of exposure and decreased in frequency and severity thereafter, paronychia occurred at a higher incidence after one year of selumetinib exposure and a higher incidence of CTCAE Grade ≥ 2 events were observed in the second year of treatment.

The adult hyd-sulfate safety pool demonstrated less frequency and severity of paronychia with a 1% (1/79) incidence rate and no Grade 3-4 events. In addition to pediatric patients being more prone to paronychia than adults, the much higher incidence rate in the pediatric pool is reflective of the longer pediatric exposure time and frequency of late onset paronychia events.

8.2.5.2 Alopecia [Reported Term of Hair Thinning] and Hair Colour Changes

Data:

See the Applicant's Position below.

The Applicant's Position:

Based on the data in pediatric and in adult patients, this medical concept of hair changes (includes the PT of alopecia and hair colour changes) was considered as an ADR for selumetinib.

In the Pediatric pool, 22 (29.7%) patients reported at least 1 AE of alopecia and 20 (27%) patients reported at least 1 AE of hair colour changes; 13 of 74 patients (17.5%) experienced both alopecia (reported term: hair thinning) and hair colour changes (reported term: hair lightening or lightening of hair color). All the reported AEs were Grade 1 and did not require dose interruption or reduction. A higher number of hair change cases were noted in Pediatric pool compared with the known safety data in adult cancer patients. In the Adult monotherapy pool a total of 21 (6.1%) patients reported AEs in the medical concept of Hair changes (PT alopecia [reported term: hair thinning] 16 [4.6%] patients, PT hair colour changes 7 [2.0%] patients). While generally hair changes are noted in pediatric populations, it is unclear why hair changes may be more prominent or more frequently observed in pediatric patients on selumetinib than in adult patients.

Schad et al 2010 have observed reduced pigmentation of hair in patients with unresectable melanoma Stage III/IV treated with 100 mg BID dose of selumetinib. This was correlated with selumetinib treatment, with repigmentation occurring upon treatment discontinuation. Similar

findings have been seen in patients treated with c-Kit–inhibiting agents (Moss et al 2003). Inhibition of c-Kit leads to reduced mitogen-activated protein kinase activity and a diminished expression of its downstream transcription factor microphthalmia-associated transcription factor (regulating the expression of tyrosinase mRNA), which regulates both melanocyte proliferation and melanogenesis.

The FDA’s Assessment:

The FDA grouped alopecia, hair color change, and hair disorder PTs for the analysis. Using this grouping, 39% (29/74) of patients in the pediatric pool and 6% (5/79) of patients in the adult hyd-sulfate pool experienced a hair disorder adverse reaction during selumetinib exposure. There were no Grade 3 or higher hair disorder AEs in either population. The FDA did not review the referenced literature regarding potential drug mechanism for this ADR.

8.2.5.3 Ejection Fraction Decreased

Data:

See the Applicant’s Position below.

The Applicant’s Position:

Clinical programs for MEK inhibitors have all included monitoring of left ventricular function with multigated acquisition or echocardiography (patients with a history of clinically significant cardiovascular disease were excluded from participating in clinical trials). Asymptomatic or symptomatic LVEF decrease/left ventricular dysfunction is generally fully reversible with discontinuation of MEK inhibition or with dose reduction when the dysfunction is not severe or symptomatic (Flaherty et al 2012a; Flaherty et al 2012b; Abdel-Rahman et al 2015; Banks et al 2017).

In SPRINT Phase II Stratum 1, AEs in the sub-group term of ejection fraction decreased events were reported for 22.0% (11 of 50) patients which were all CTCAE Grade 2, no events of a higher CTCAE Grade severity reported. The median time to first onset of AEs in the sub group term of ejection fraction decreased events was 226.0 days, with a median duration of 77.5 days. None of the events resulted in dose modification or discontinuation, and where event outcome was known (8 patients), all patients recovered.

All cases of ejection fraction decreased in the Pediatric pool were identified during routine investigations. These were not accompanied by symptoms suggestive of cardiac failure/impairment, such as edema, dyspnea, palpitations, fatigue, or syncope. The majority of AEs of ejection fraction decreased were a numerical reduction which met the criteria value as a decrease from baseline but remained in the normal range.

As pediatric patients with a history of impaired left ventricular function or a baseline LVEF below institutional LLN have not been studied, labelling guidance suggests LVEF should be

evaluated before initiation of treatment to establish baseline values and ensure that they are above the LLN. Reduction in LVEF can be managed using treatment interruption, dose reduction or treatment discontinuation.

The FDA's Assessment:

The FDA agrees with the summary data provided by the Applicant for EF decreases observed in SPRINT Phase II Stratum 1 and notes that the Applicant submitted corrected data for resolution rates for EF decrease events subsequent to the analysis described above. Of the 11 patients with EF decreases, 6 recovered and 5 had unknown outcomes.

Across the pediatric pool, 17% (23/74) of patients experienced EF decrease including one Grade 3 LVEF decrease (EF decrease from 65% to 50%) resulting in dose reduction. All EF decrease events were asymptomatic and detected on routine echocardiograms performed during the study. During SPRINT, a numerical drop of 10% or more from baseline was counted as an EF decrease AE. Fourteen of the 17 patients who experienced EF decrease maintained EFs that met the study entry criterion of $EF \geq 53\%$. The other 3 patients had an EF decrease to 50% (n=2) or 52% (n=1).

In adult selumetinib studies, EF decrease events were generally considered AEs if the EF decreased below the institutional lower limit of normal. In the adult hyd-sulfate pool, 3% (2/79) of patients experienced left ventricular dysfunction AEs. Both events were Grade 3 and resulted in permanent discontinuation of selumetinib. Both patients recovered. Across the larger adult monotherapy pool, there were two grade 5 cardiac events: congestive heart failure and cardio-respiratory arrest. These events are described in Section 8.2.4 under Deaths.

Ventricular dysfunction, including EF decrease, is a known MEK inhibitor-related toxicity. During SPRINT, patients underwent baseline echocardiogram and then routine echocardiograms every 4 cycles for the first year of treatment and every 6 cycles thereafter. There were specific management guidelines for providers based on the level of LVEF decrease and whether the patient was symptomatic. Pediatric cardiology consultation was the usual course of action. Sections 2 and 5 of the product label will provide similar guidelines for prescribers.

8.2.5.4 Blood CPK Increase

Data:

See the Applicant's Position below.

The Applicant's Position:

Effects on muscle function have been identified as an AESI with selumetinib treatment. In general, muscle function events were mild or moderate in severity, rarely led to treatment

discontinuation, were manageable by standard therapies, and generally resolved during continued treatment with selumetinib.

In the Pediatric pool, AEs in the sub-group term of CPK increased events were reported by most patients (87.8%; 65 of 74 patients). AEs were predominantly CTCAE Grade 1 or Grade 2 (74.3% patients); with few patients reporting AEs of CTCAE Grade 3 (6.8%) or CTCAE Grade 4 (4.1%). The median time to first onset of AEs in the sub-group term of CPK increased events was 84.0 days, with a median duration of 143.0 days.

In SPRINT Phase II Stratum 1, 38 (76.0%) patients experienced an AE of blood CPK increased. For the maximum CTCAE grade events that patients experienced, the median time to onset was 105.5 days and the median duration was 126.0 days. The majority of events were Grade 1 or 2 and resolved with no change in selumetinib dose. CTCAE Grade ≥ 3 events occurred in 3 (6%) patients and 1 (2.0%) patient (Patient (b) (6)) had an AE of CTCAE Grade 4. Only 1 (2.0%) patient (Patient (b) (6)) in SPRINT Phase II Stratum 1 had an AE which led to selumetinib dose interruption followed by dose reduction; none of the AEs required dose discontinuation.

CPK increased is not uncommon in children. CPK levels are known to transiently rise after physical activity. The degree of CPK elevation depends on the type and duration of physical activity, with greater elevation in those who do not do such activity consistently (Moghadam-Kia et al 2016). There are also reports which suggests that there is a small reduction in CPK levels as people age (Lilleng et al 2011). There was no evidence of muscular AEs such as myalgia or muscular weakness in association with selumetinib-induced CPK increases, with the exception of a small number of reports where other more plausible aetiologies such as vertebral disc prolapse and muscle exertion were identified.

The FDA's Assessment:

The FDA agrees with Applicant's analysis of CPK events across the pediatric pool. The PTs included in the 88% event rate were CPK elevation, musculoskeletal pain, muscular weakness and myalgia. The FDA does not fully agree with the Applicant's discussion of CPK elevation in children as compared to adults. While the FDA acknowledges that CPK levels may be higher after physical activity, the Moghadam-Kia reference also notes that levels normalize in most patients within seven days of onset which was not typical when CPK elevation duration was assessed in the pediatric pool.

Rhabdomyolysis is a rare and serious adverse reaction associated with the MEK inhibitor class. The FDA reviewed pediatric and adult safety data for rhabdomyolysis, CPK elevation, and CPK elevation that was concurrent with muscle symptoms and/or renal dysfunction. Given the relatively small pediatric safety pool in the original NDA and the short median exposure time for the 79 adult patients who received the hyd-sulfate formulation, the FDA requested that the Applicant submit additional analyses of CPK elevation and rhabdomyolysis using the global adult safety database, selumetinib expanded access program in PN, and externally-sponsored

selumetinib studies. The following analyses of rhabdomyolysis and CPK elevation consider the review of these data sources in addition to the pediatric and adult monotherapy datasets in the original NDA.

Rhabdomyolysis

There were no events of rhabdomyolysis in the pediatric pool or in pediatric patients treated in externally-sponsored studies, or in the selumetinib PN expanded access program. The Applicant identified two cases of rhabdomyolysis in adult patients across 36 externally-sponsored trials. Both patients received selumetinib during Study D1532C00049, an NCI-sponsored study of selumetinib monotherapy in adult patients with relapsed/refractory multiple myeloma.

Patient (b) (6): 69 yo with myeloma and medical history significant for prior chemotherapy, stroke, prostate cancer, and rheumatoid heat disease, presented after three weeks of selumetinib exposure with chest pain and Grade 4 thrombocytopenia. He developed acute renal failure (creatinine of 5.4 mg/dL) three days later. He was diagnosed with rhabdomyolysis 5 days later. No CPK values were provided. The patient was hospitalized, had a negative sepsis workup, was started on dialysis, and received plasmapheresis for 2 days. His creatinine continued to rise, and he went into respiratory failure, was transferred to hospice care and died. The events of rhabdomyolysis, acute kidney injury, and decreased platelet count were considered related to both selumetinib and to progression of primary disease by the investigator.

Patient (b) (6): 77 yo with multiple myeloma and medical history significant for prior chemotherapy, immunotherapy and hematopoietic stem cell transplantation, presented to clinic after a 2 month exposure to selumetinib and laboratory assessments showed elevated BUN and creatinine, myoglobin increase (308 ng/mL) and CPK increase (427 IU/L). The patient was hospitalized for Grade 3 rhabdomyolysis and acute kidney injury. Selumetinib was discontinued. The patient was treated with intravenous fluids, and both CPK and myoglobulin levels were reported to have decreased. The patient improved and was discharged after 3 days. The investigator attributed the kidney injury and rhabdomyolysis to selumetinib.

Reviewer: *While both of these cases are confounded by the patients' underlying disease, the reviewer agrees with the investigators' assessments. Given the known safety profile of the MEK inhibitor class, selumetinib should be considered at least possibly related to these rhabdomyolysis events.*

CPK elevation

Across the pediatric pool, CPK elevation occurred in 76% (56/74) of patients including 10% (7/74) of patients with $\geq$ Grade 3 CPK increases and 3% (2/74) of patients with Grade 4 CPK elevation. Two patients had SAEs of CPK elevation, and these cases are discussed in Section 8.4.2 under SAEs. There were no permanent discontinuations for CPK elevation. Seven percent

(5/74) of patients required dose reductions for Grade 3 or 4 CPK elevation. The median time to onset of CPK elevation was 106 days and the median duration of CPK elevation was 95 days.

Eleven patients (15%) in the pediatric pool experienced concurrent ($\geq$ one day overlap) CPK and creatinine increases at least once including 3 patients from SPRINT Phase II Stratum 1 who experienced concurrent or subsequent (within 30 days) muscle symptoms. Of these, 1 patient (b) (6), reported musculoskeletal pain concurrent with blood CPK increase and creatinine increase and is described below. In the other 2 patients, the musculoskeletal pain occurred concurrently with Grade 1 creatinine elevation, but there was no overlap with increased CPK.

Patient (b) (6): Grade 2 musculoskeletal pain occurred concurrently with Grade 1 CPK elevation and Grade 2 creatinine increased. The overlap between musculoskeletal pain and blood CPK increased was 1 day; the overlap between musculoskeletal pain and blood creatinine increased was for 29 days. The investigator assessed the musculoskeletal pain as not related to selumetinib and the CPK increase as related. The events resolved without dose modification.

Five patients (7%) experienced myalgia or muscle weakness concurrent with CPK elevation. None of these patients showed evidence of renal dysfunction.

Patient (b) (6): Grade 1 myalgia concurrent with Grade 1 blood CPK increased for 6 days. Both resolved without dose modification and were attributed by the investigator to patient carrying a heavy back pack and to selumetinib.

Patient (b) (6): Two Grade 1 myalgia events overlapped with ongoing Grade 1 CPK elevation. The investigator considered both events of myalgia as unrelated to selumetinib.

Patient (b) (6): This patient experienced multiple events of myalgia, muscular weakness and CPK elevation during the study. There was one Grade 3 event of muscle weakness that was concurrent with Grade 1 CPK elevation that resolved. There was one isolated event of Grade 3 CPK elevation resulting in dose reduction. The investigator attributed CPK elevation to selumetinib; the muscle weakness was attributed to a disc prolapse.

Patient (b) (6): Three AEs of Grade 1 myalgia including one event that overlapped with an ongoing Grade 1 CPK elevation. Both events resolved without dose modification. The investigator attributed both events to selumetinib treatment.

Patient (b) (6): This case is summarized under Section 8.2.4 Discontinuation AEs.

Reviewer: *CPK elevation was common in pediatric patients exposed to selumetinib; however, there were no rhabdomyolysis events reported in the pediatric population. Patients who experienced concurrent CPK elevation and creatinine elevation and/or muscle symptoms*

generally had Grade 1-2 events that resolved without dose reduction. CPK elevation rates were not reliable in the adult monotherapy pool because not all studies required routine assessments. There were rare cases of rhabdomyolysis in the adult global data. Given the risks for CPK elevation and rhabdomyolysis with MEK inhibitors, the FDA included CPK elevation as a warning in Section 5 of the product label with specific dose modification guidelines in Section 2.

8.2.5.5 Blurred Vision (Visual Disturbances)

Data:

See the Applicant's Position below.

The Applicant's Position:

Ocular toxicity including vision blurred, csr, retinal pigment epithelial detachment (RPED) and RVO is a known ADR for selumetinib monotherapy and all adult and pediatric protocols contained specific toxicity management guidelines in place for management of these events. A detailed analysis of AEs within retinal events (consisting of the standardised MedDRA query of retinal disorders, RPED events, csr events, RVO events, other retinal disorders) was performed. Retinal events that were reported by 2 or more patients in the SPRINT Phase II Stratum 1 data included vision blurred (4 of 50 patients, 8.0%) and photophobia (2 of 50 patients, 4.0%), which were reported at a similar frequency in the Pediatric pool.

Effects on the eye have been identified as an AESI with selumetinib treatment. In general, retinal effects were mild or moderate in severity, did not lead to treatment discontinuation, were manageable by standard supportive therapies, and generally resolved during continued treatment with selumetinib.

Blurred vision has been reported in both pediatric and adult populations; events were generally CTCAE Grade 1. AEs consistent with csr/RPED and with RVO have also been reported in a small number of patients receiving treatment with selumetinib, generally in combination with other anti-cancer agents targeting AKT inhibition or IGFR-IR inhibition, or with cytotoxic chemotherapies. Blurred vision was reported by 4 patients (8.0%) in SPRINT Phase II Stratum 1 and at a similar frequency in the Pediatric pool (9.5%). The median time to onset of blurred vision in SPRINT Phase II Stratum 1 was 455.5 days, and the event rate (per 100 patient years) was 4.03.

AEs in the sub-group terms of RVO events, csr events, and RPED events were not reported for any patients in the Pediatric pool.

Within the subgroup term of RVO events, csr events, and RPED events, no events were reported for any patients in the Pediatric pool. This was consistent with the observation that no retinal involvement was observed in the ophthalmic examinations of pediatric patients. In

adults an isolated case of RVO was reported (after double-blind treatment with selumetinib + dacarbazine in the Study D1344C00001).

Guidance in the proposed label advises that,

(b) (6)

The FDA's Assessment:

The FDA agrees with the Applicant's incidence rates for retinal and visual AEs in SPRINT Phase II Stratum 1.

Ocular toxicity is an adverse reaction associated with the MEK inhibitor class. RVO is rare, but can result in blindness. RPED, a retinal detachment at the retinal pigment epithelium layer, includes central serous retinopathy (CSR), chorioretinopathy, and detachment of the retinal pigment epithelium events. Other more common ocular AEs associated with MEK inhibition include blurred vision, periorbital edema and dry eyes.

The FDA reviewed the pediatric and adult safety pools data for retinal AEs, visual impairment, and other ocular AEs. Given the rarity of some serious ocular AEs (RVO, RPED) and the relatively small pediatric safety pool, and the short median exposure time for the adult data pool, the FDA requested that the Applicant provide additional analyses of ocular toxicity across the global adult safety database, selumetinib expanded access program, and externally-sponsored selumetinib studies. The following analyses consider the review of these data sources in addition to the pediatric and adult monotherapy data pools in the original NDA.

Across the pediatric pool, 33% (24/74) of patients experienced at least one eye disorder AE (PTs included in Eye disorders SOC). There were no SAEs, AEs $\geq$ Grade 3, discontinuation AEs or dose reductions for ocular toxicity in the pediatric pool. In the adult hyd-sulfate pool, 27% of patients experienced an eye disorder during selumetinib including one Grade 3 visual impairment and one Grade 2 RVO resulting in discontinuation of selumetinib. Five percent (4/79) of adult patients experienced RPED or chorioretinopathy. These events were not serious or severe and did not result in dose modification. See Table 56.

Table 55 Ocular Toxicity, Pediatric Pool and Adult Monotherapy Pool

AE Category	Pediatric Pool N=74 n (%)	Adult Pool N=79 n (%)
Any Ocular AE	24 (33)	27 (36)
Serious AE	0	0

AE Category	Pediatric Pool N=74 n (%)	Adult Pool N=79 n (%)
Grade $\geq$ 3 AE	0	1 (1)
AE $\rightarrow$ Discontinuation	0	1 (1)
AE $\rightarrow$ Dose reduction	0	0
Retinal AEs	1 (1)	5 (6)
Chorioretinal scar	1 (1)	0
Retinal vein occlusion	0	1 (1)
RPED/retinal detachment	0	2(3)
CSR/chorioretinopathy	0	2 (3)
Retinal tear	0	1 (1)
Visual AEs	11 (15)	14 (18)
Blurred vision	7 (9)	10 (13)
Photophobia/photopsia	3 (4)	1 (1)
Vitreous Strands	1 (1)	1 (1)
Visual impairment	0	3 (4)
Other Ocular AEs		
Increase lacrimation	9 (12)	3 (4)
Dry Eye	4 (5)	2 (3)
Periorbital edema ¹	4 (5)	8 (10)
Ocular hypertension	1 (1)	0
Cataract	1 (1)	0

Source: ISS Pediatric pool ADAE.xpt

¹Periorbital edema: eye edema; eye swelling; eyelid edema; periorbital edema

The FDA reviewed the selumetinib expanded access program data and the externally-sponsored pediatric studies data for additional pediatric ocular toxicities. In the PN expanded access program, 3 pediatric patients had ocular SAEs (visual field defect, eye disorder, abnormal ocular finding). The patient with the visual field defect discontinued selumetinib. In the pediatric external study dataset, 2 patients experienced optic nerve disorders resulting in discontinuation, and one patient experienced RPED (see summary narrative below). The FDA notes that this dataset is confounded by patients having underlying low grade glioma, and in some cases, existence of baseline visual impairments due to underlying disease.

RPED SAE: 13 yo with pilocytic astrocytoma affecting the optic nerve presented during Cycle 6 with vision impairment. According to the narrative, gross examination of the eyes was

unremarkable. An undilated fundal examination revealed mild hyperlucent pigmentary changes in the central macula bilaterally. The visual fields were full in the left eye and diminished in the infratemporal portion of the right eye. On optical coherence tomography (OCT) the macula revealed the beginning of the separation of the retinal pigmented epithelium in both eyes at the fovea. Selumetinib was discontinued. The patient recovered. The ophthalmologist considered the retinal detachment causally-related to selumetinib.

The Applicant's search of the adult global database of 1860 patients who received selumetinib as single agent or in combination with other agents revealed 0.2% (4/1860) patients with RVO and 0.1% (1/1860) RPED events. The four patients who experienced RVO events had Grade 2 (n=3) or Grade 1 (n=1) events. These patients were treated with combination regimens. Two of the 4 patients are reported to not have recovered. Across the externally-sponsored adult studies, there was an additional RVO event and 6 RPED events with limited information regarding outcomes.

***Reviewer:** Selumetinib appears to have a similar ocular risk profile as other commercially available MEK inhibitors. While serious toxicities such as RVO and RPED occurred rarely in the pediatric data, there is no evidence that pediatric patients have less risk than adult patients for MEK-associated retinal AEs. An FDA ophthalmology consult was obtained to make recommendations on mitigating risk for serious ocular toxicity. These recommendations are included in Sections 2 and 5 of the product label.*

8.2.5.6 Rash

Data:

See the Applicant's Position below.

The Applicant's Position:

Acneiform rash and other (non-acneiform) rashes have been identified as AESIs with selumetinib treatment. The pediatric study protocols had specific toxicity management guidelines in place for management of these events.

In the Pediatric pool, the AEs in the grouped term of acneiform rash were reported for 54.1% (40 of 74) patients, all of which were the term of dermatitis acneiform. AEs were predominantly CTCAE Grade 1 or Grade 2 (38 [51.4%] patients) with few (2 [2.7%]) patients reporting CTCAE Grade 3 dermatitis acneiform. The median time to first onset of AEs in the grouped term of acneiform rash was 27.0 days, with a median duration of 111.0 days. Observation regarding the incidence, severity, time to onset and duration of acneiform rash were similar in the SPRINT Phase II Stratum 1. Generally, it was observed that acneiform rash was observed in postpubertal patients (>12 years). Dermatitis acneiform occurred at a higher

frequency in patients aged 12 to 16 years of age (95.8%, 23 of 24 patients) compared to patients aged ≥ 2 to 11 years (26.7%, 12 of 45 patients).

In the Pediatric pool, AEs in the grouped term of non-acneiform rash were reported for 64.9% (48 of 74 patients, patients predominantly pruritus (41.9%) and rash maculopapular (39.2%). AEs were predominantly CTCAE Grade 1 or Grade 2 (46 [62.2%] patients); 2 (2.7%) patients had AEs of CTCAE Grade 3. The median time to first onset of AEs in the grouped term of non acneiform rash was 190.5 days, with a median duration of 34.0 days. Observation regarding the incidence, severity, time to onset and duration of acneiform rash were similar in the SPRINT Phase II Stratum 1.

The FDA's Assessment:

Skin toxicity is part of the safety profile of MEK inhibitors. The FDA's analysis of rash was based on data from the pediatric pool and the adult hyd-sulfate pool. The search strategy for relevant PTs included use of the following HLTs: acnes, bullous conditions, dermatitis and eczema, erythemas, exfoliative conditions, rashes, eruptions and exanthems, and urticarias. Rashes were very common during SPRINT. The majority of rashes were Grade 1-2 and did not require dose modification. There were no SAEs and no discontinuations due to rash. Three patients required dose reduction for Grade 3 maculopapular rash (n=2) and Grade 3 urticaria (n=1).

Dermatitis acneiform occurred in more than half of the patients, and as the Applicant notes, was more prevalent in the adolescent population. In the age subgroup 2-11 years, 27% (12/45) of patients experienced dermatitis acneiform. In patients older than 12 years, 97% (28/29) developed acneiform rash during selumetinib exposure. Table 57 summarizes the various rashes that occurred in the pediatric pool.

Table 56 Summary of Rashes, Pediatric Pool

Rash Category	Any Grade N=74 n (%)	Grade 3-4 N=74 n (%)
Any Rash	67 (91)	6 (8)
Acneiform Rash	40 (54)	2 (3)
Nonacneiform Rashes	48 (65)	4 (5)
Eruptions/Exanthems/Urticarias		
Rash maculopapular	15 (20)	1 (1)
Erythema ¹	9 (12)	0
Exfoliative rash	6 (8)	0
Urticarias	4 (5)	1 (1)
Rash	3 (4)	0
Dermatitis and Eczema		
Eczema ²	21 (28)	2 (3)
Dermatitis contact	2 (3)	0
Seborrheic dermatitis	2 (3)	0
Dermatitis ³	2 (3)	0
Dermatitis bullous	1 (1)	0
Dermatitis diaper	1 (1)	0

Source: ISS Pediatric pool ADAE.xpt

¹Erythema includes erythema; rash erythematous

²Eczema includes eczema; atopic dermatitis

³Dermatitis includes dermatitis; skin irritation

There were no events of palmar-plantar erythrodysesthesia syndrome (PPES) in the pediatric pool. Pruritis occurred in 43% (32/74) of patients in the pediatric pool. Pruritis events were nonserious and Grade 1-2 in severity. One patient required dose reduction for pruritis.

Among the adult patients who received the hyd-sulfate capsule, 73% (58/79) experienced at least one rash AE during selumetinib exposure including 8% (6/79) Grade 3 rashes. Similar to the pediatric pool, dermatitis acneiform was common and occurred in 35% (28/79) of patients including one Grade 3 rash that resulted in permanent discontinuation of selumetinib. PPES occurred in 6% (5/79) of patients including one Grade 3 event requiring interruption of selumetinib. Pruritis occurred in 14% (11/79) of patients, and all events were Grade 1-2.

Skin Rash and Associated Infections

Across the pediatric pool, concurrent rashes and skin infections were not common, and in the cases where these events occurred in a temporal relationship, causality was confounded (e.g. staphylococcal infections in patients with underlying chronic eczema, ringworm). The Applicant provided an analysis of concurrent skin rashes and infections across the adult monotherapy pool of 347 patients. Six percent (21/347) had concurrent rash and skin infection or skin infection events within 30 days of rash. All infections were Grade 1-2 except for one patient with an SAE of Grade 3 cellulitis

Patient (b) (6): 58 yo male developed diffuse rash on Day 11 which was present for 50 days. Approximately 4 weeks after the rash started, the patient experienced Grade 3 right leg cellulitis. The patient presents with fever, cellulitis and associated lymphedema of the right leg. Selumetinib was interrupted. While the patient was in the hospital, imaging revealed progressive disease, and the patient did not restart selumetinib. The patient recovered from right leg cellulitis.

Reviewer: *Skin toxicities including dermatitis acneiform, nonacneiform rashes, pruritis and dry skin were common during selumetinib treatment. The majority of events were Grade 1-2 in severity and did not require dose modifications in pediatric patients. Despite the frequency of rashes, it did not appear that rashes led to serious skin infections in patients with NF1 PN. PPES did not occur in the pediatric population; however, this is a known risk with MEK inhibitors and other targeted agents. This toxicity was observed in the adult selumetinib data. Given the frequency of skin toxicity associated with selumetinib, the product label includes a warning in Section 5 and specific dose modification guidelines in Section 2.*

8.2.5.6 Physeal Dysplasia

Data:

See the Applicant's Position below.

The Applicant's Position:

Physeal dysplasia has been identified as a potential risk for selumetinib treatment, based on data from nonclinical studies. No AEs of physeal dysplasia were reported for the Pediatric pool or for the Adult monotherapy pool. In order to ascertain the risk of physeal dysplasia, height was used as a surrogate to ascertain the effect of selumetinib on growth plates.

Data of the growth centiles from the Pediatric pool were overlaid with the growth centiles from patients on the Natural history study, which acted as a control population. Based on this data, selumetinib does not appear to have any adverse effects on skeletal growth in patients enrolled in SPRINT. This data is also supportive of an independent data analysis done for the SPRINT Phase I data by NCI/CTEP.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment and notes that growth and development parameters will continue to be monitored as part of the long-term safety follow-up for SPRINT and as part of the post-marketing requirements for selumetinib.

8.2.5.7 Serious Gastrointestinal Toxicity

The FDA's Assessment:

GI toxicity is part of the safety profile of the MEK inhibitor class. Serious GI toxicity is a labeled warning in the trametinib package insert based on observed events of colitis and fatal GI perforation. Colitis is labeled as an important adverse reaction in the binimetinib package insert. Given the class safety signal and the observation of frequent GI toxicity during SPRINT, the FDA considers GI toxicity to be an additional AESI for selumetinib.

Across the pediatric pool, GI toxicity was common. The FDA acknowledges the relatively long median exposure time to selumetinib and that diarrhea, vomiting and abdominal pain are more common complaints in a pediatric population as compared to adults. FDA therefore considered severity of the events, impact on dosing, the investigators' assessments of relatedness, and events per patient in the overall risk assessment.

Diarrhea occurred in 77% of patients including 15% with Grade 3 events. One patient required dose reduction followed by permanent discontinuation for diarrhea. Investigators assessed diarrhea as possibly or probably related to selumetinib in 65% (48/74) of patients. The median number of diarrhea AEs per patients was 4 (range: 1-29). Per protocol, patients on SPRINT started loperamide or other anti-diarrheal agents at the onset of the first loose stool.

Vomiting occurred in 82% (61/74) of patients including 8% with Grade 3 events. Vomiting AEs did not result in discontinuation or dose reductions, but 25% of patients required drug interruptions for vomiting. Investigators assessed vomiting as possibly or probably related to selumetinib in 72% (53/74) of patients. The median number of vomiting AEs per patients was 4 (range: 1-20).

Stomatitis was also common in the pediatric pool. Fifty percent of patients experienced at least one occurrence of stomatitis; however, there were no $\geq$ Grade 3 events.

Serious GI toxicity in the pediatric pool was uncommon. There were no intestinal obstruction or perforation events during SPRINT. One patient had two episodes of colitis that were considered unrelated to selumetinib and possibly related to prior antibiotic use. One of the events was Grade 3 and required hospitalization for intravenous fluids, metronidazole and vancomycin.

Given the rarity of some serious GI toxicities, the relatively small pediatric safety pool, and the short median exposure time for the adult monotherapy pool, the FDA requested that the

Applicant provide additional analyses of serious GI toxicity including colitis, ileus, intestinal obstruction and intestinal perforation, across the global adult safety database, selumetinib PN expanded access program, and externally-sponsored selumetinib studies.

Serious GI Toxicity: Global Database

The Applicant conducted an analysis of the safety database for AZ-sponsored trials of selumetinib as a single agent or in combination using preferred terms included under the GI Disorders SOC and SMQ for gastrointestinal perforation, ulceration, hemorrhage or obstruction. Using this search strategy, among 1449 patients, 8% (113/1449) experienced GI SAEs including 0.4% (6/1449) Grade 5 events. Four percent (55/1449) of patients experienced SAEs considered at least possibly related to selumetinib. The following causally related SAEs occurred in more than one patient: abdominal pain (N=5, 0.3%), colitis (N=3, 0.2%), and ileus (N=2, 0.1%). Four patients experienced fatal events deemed related to selumetinib: chemical peritonitis, abdominal pain, hematemesis, and upper GI hemorrhage. Except for one Grade 5 abdominal pain event ((b) (6)), discussed in Section 8.2.4 under Deaths), all other Grade 4 and 5 SAEs occurred in patients receiving selumetinib as part of combination regimens.

Grade 5 Events

Patient (b) (6): Grade 5 abdominal pain. See Section 8.2.4 under Deaths

Patient (b) (6): Grade 5 Upper Gastrointestinal Hemorrhage. 68 yo male with metastatic Stage IV NSCLC with pleural effusion. Relevant concomitant medications included omeprazole, sodium picosulfate, morphine, ondansetron, metoclopramide, and loperamide. The patient presented with Grade 3 diarrhea on Day 2. The patient had blood in his stool. He was hospitalized for IV fluids and electrolyte replacement. Hb was 8.6, decreased from enrollment Hb of 10.9. Endoscopy was performed and showed no sites of active bleeding and he was diagnosed with nonerosive gastritis. The diarrhea resolved. On Day 33, the patient experienced upper gastrointestinal hemorrhage, with profuse bleeding through the nose and mouth at home followed by hematemesis and death. The primary cause of death was upper digestive tract bleeding and the secondary cause of death was NSCLC. Autopsy was not performed. Investigator assessed the event as related to selumetinib and unrelated to docetaxel.

Reviewer: *Selumetinib cannot be excluded from causality analysis, but this case is confounded by the presence of baseline gastritis at enrollment.*

Patient (b) (6): *Grade 5 chemical peritonitis/gastrointestinal perforation.* 67 yo male with metastatic NSCLC. Medical history significant for completion of 6 cycles of cisplatin and pemetrexed one month prior to initiation of selumetinib and docetaxel. The patient was diagnosed with chemical peritonitis on Day 66. He received metronidazole, nefopam and paracetamol. An endoscopy was performed and biliary peritonitis was observed but no perforation was reported. The investigator assessed the peritonitis with pneumoperitoneum to be associated with gastrointestinal perforation leading to septic shock and acute renal failure.

The cause of death was initially reported as peritonitis; however, on follow-up report, the cause of death was changed to gastrointestinal perforation 'not proved'. Autopsy was not performed. The investigator assessed the fatal event as related to selumetinib and docetaxel.

Reviewer: *Selumetinib cannot be excluded in the causality analysis; however, there is limited information to make a reliable assessment in this case. Peritonitis and pneumoperitoneum could certainly lead to intestinal perforation and septic shock. It is not clear how the patient presented at the time of diagnosis with peritonitis or when the endoscopy was preformed relative to the patient's death.*

Patient (b) (6): Grade 5 hematemesis. 84 yo male with metastatic NSCLC treated with prior carboplatin and paclitaxel. On Day 42, the patient had Cycle 3 lab assessment showing Hb 9 g/dL, INR 1.03, P 12.1 seconds and platelet count of 177. On Day 46, the patients had Grade 2 vomiting for 3 days which was reported as resolved. On Day 52, the patient experienced hematemesis and was taken to the emergency room. The hematemesis worsened and the patient was reported to have died on the same day. No endoscopy was performed. The causes of death were reported as lung cancer, multiple organ failure and hematemesis. Autopsy was not performed. The event hematemesis was assessed by the investigator as related to selumetinib and docetaxel.

Reviewer: *There is insufficient information to make a definitive causal assessment, but selumetinib cannot be excluded from the attribution analysis.*

Grade 4 SAEs

The Applicant's search also identified a Grade 4 gastric ulcer perforation event and a Grade 4 ileus event that were serious and considered causally related to selumetinib.

Patient (b) (6): *Grade 4 gastric ulcer perforation.* 60 yo male with metastatic NSCLC and medical history significant for gastritis, diabetes, HTN, and 8 prior cycles of etoposide and cisplatin. The patient experienced Grade 3 vomiting on Day 86 and docetaxel was discontinued. On Day 125, the patients was admitted with an acute abdomen and diagnosed intraoperatively with a Grade 4 gastric ulcer perforation. The patient was transferred to the ICU and was also being treated for a Grade 2 pneumonia. The patient improved and was discharged after 29 days in the hospital. The event of gastric ulcer perforation was assessed by the investigator as related to selumetinib but not docetaxel and resulted in discontinuation.

Patient (b) (6): Grade 4 ileus. 60 yo male with NSCLC with adrenal and brain metastases. Medical history significant for ileus and hernia repair and prior cisplatin and pemetrexed. The patient was taking metoclopramide for nausea and naloxone for pain. On Day 23, the patient was hospitalized for Grade 4 ileus and underwent surgery with ileal resection the next day. Immunohistochemistry analysis of the tissue showed findings which were consistent with metastasizing adenocarcinoma. Selumetinib was discontinued on Day 23. Four days after the

surgery, the patient developed sepsis and died. No autopsy was performed. The investigator assessed the ileus and the sepsis as related to both selumetinib and docetaxel.

Reviewer: There are confounders in both of these cases, particularly the finding of a developing metastatic lesion in the ileum in the latter patient; however, given that MEK inhibitors are known to be associated with serious GI toxicities including perforation, selumetinib cannot be excluded as a potential causal factor in either event.

Serious GI Toxicity: Expanded Access Program and Externally-Sponsored Trials

There were no events of ileus, intestinal obstruction or intestinal perforation in the selumetinib PN expanded access program. There was one serious colitis event in the context of sepsis and UTI diagnosed the same day and considered unrelated to selumetinib by the investigator.

There were 11 events of colitis, ileus, intestinal obstruction or intestinal perforation events from externally-sponsored research studies including one fatal intestinal obstruction, one colitis in a pediatric patient, and one intestinal obstruction in an adult patient with PN. Limited information was available for these events. The fatal obstruction event was considered unrelated to selumetinib and related to progressive metastatic cervical cancer. The colitis event was Grade 3, assessed as infectious and unrelated to selumetinib, and the patient recovered. The patient with PN experienced nausea and Grade 3 small intestinal obstruction 9 days after starting selumetinib. The investigator considered the events unrelated to selumetinib

Reviewer: *In summary, GI toxicity is MEK inhibitor class effect. GI toxicity during the SPRINT trial was frequent but usually tolerable and patients were managed per protocol with supportive care measures and interruptions. Serious GI toxicities including perforation, obstruction and hemorrhage events were not observed across the pediatric pool which had relatively long exposure to selumetinib. However, more serious GI toxicities were identified across the global selumetinib datasets. The incidence was rare, but selumetinib was considered causally related in the events summarized above. The FDA considers that the pediatric PN population under the labeled indication is at risk for developing serious GI toxicity associated with use of selumetinib and should be monitored carefully. The product label attempts to mitigate risk by including specific precautions and dose modification guidelines. Additionally, this risk will be continually assessed during the long-term follow up of pediatric patients with PN in the post marketing phase.*

8.2.5.8 Hemorrhage

Hemorrhage is a labeled warning in commercially available MEK inhibitors including trametinib, binimetinib and cobimetinib. The safety data demonstrating this risk was mostly from the MEK inhibitor given in combination with a BRAF inhibitor. Rare, but serious hemorrhage events including GI bleeding, intracranial hemorrhage and hematuria are described in association with

use of these agents. The FDA therefore conducted analyses to assess bleeding/hemorrhage events across the pediatric and adult single agent safety pools.

Across the pediatric pool, 53% (39/74) of patients had some bleeding event including the following preferred terms: anal hemorrhage, ecchymosis, epistaxis, hematochezia, hematoma, hematuria, lower gastrointestinal hemorrhage, menorrhagia, oligomenorrhea, and rectal hemorrhage. Among these, 22% (16/74) had a bleeding event that was considered at least possibly related to selumetinib exposure including epistaxis (n=9) hematuria (n=5), anal/rectal hemorrhage (n=1) hematochezia and lower GI hemorrhage (n=1). All events were nonserious and Grade 1-2 in severity. There were two Grade 3 bleeding AEs that were considered unrelated to selumetinib: hematoma and hematuria, each in one patient, each resulting in interruption but no dose reduction.

Across the supportive adult hyd-sulfate pool, 14% (11/79) of patients experienced a bleeding event including the following preferred terms: anal hemorrhage, ecchymosis, epistaxis, GI hemorrhage, hematemesis, hematuria, hemorrhagic anemia, and vaginal hemorrhage. All events were Grade 1-2 except for two Grade 3 events of GI hemorrhage and serious hematemesis. Only one bleeding event (epistaxis) was considered related to selumetinib. Across the larger adult monotherapy pool of 347 patients, there were 3 fatal bleeding events: hemoptysis in a patient with NSCLC, ruptured aortic aneurysm which occurred 35 days after the last dose of selumetinib, and cerebral hemorrhage in a patient with brain metastases. The investigators attributed these events to underlying disease or pre-existing conditions and unrelated to selumetinib.

Among pediatric patients in the externally-sponsored research studies, there were four patients with serious bleeding events including Grade 3 hematuria (1), Grade 2 intracranial hemorrhage (2) and Grade 2 hemorrhoid hemorrhage (1). These patients all had underlying low grade glioma. The investigator assessed the Grade 2 hemorrhoid bleeding as related to selumetinib. The other events were considered unrelated. Among pediatric patients in the PN expanded access program, there were 3 serious hematuria events, no grading available, none resulting in dose modifications. One event was considered related to selumetinib.

Based on review of the available data, common bleeding events that occurred in SPRINT will be included in Section 6 of the label.

8.2.5.9 Weight Gain

The Applicant's Position:

Selected AEs of weight increased were considered to be other significant adverse events (OAEs) based on the fact that these events were managed through selumetinib dose modification by the investigator.

A total of 3 patients had an OAE of weight increased, 2 of which were considered causally related to selumetinib by the investigator. All of the events were CTCAE Grade 3, considered to be non-serious, and resulted in selumetinib dose modification: 2 patients had an interruption and 1 patient had an interruption followed by a dose reduction. Two patients recovered, and the outcome was unknown for the remaining patient.

Based on the review of data from adult studies (Study 8 and Study 12), weight gain in these patients was attributed to confounding factor of edema. Bekaii-Saab et al (2011) have shown that in a Phase II Metastatic Biliary Cancer study, patients treated with selumetinib gained an average nonfluid weight of 8.6 pounds. The authors attributed this observation to the possible immune-modulation properties of selumetinib. However, the incidence of weight increased that has been observed in SPRINT Phase II Stratum 1 (5 of 50 patients; 10%) is consistent with the frequency observed in a cross-sectional study reviewing the weight of children and adolescents (age range 0 to 19 years) with NF1 (6 of 81 patients; 7.4%) (Rockwell 2001).

The FDA's Assessment:

The FDA analyzed the pediatric pool database for weight gain that was considered a treatment emergent AE. Across the 74 patients included in the pediatric NF1 PN pool, 14% (10/74) experienced an AE of increased weight including six patients (8%) with Grade 3 weight increase AEs. One weight increase AE resulted in permanent discontinuation and two patients had dose reductions. The FDA reviewed the summary narratives of the three patients in SPRINT Phase II Stratum 1 who required dose modifications due to weight increase AEs and there were confounding variables and unknowns (e.g., diet changes) in all cases. The literature reference provided to support the assertion that weight gain in SPRINT was consistent with that of the NF1 general pediatric population is based on a cross sectional study in Brazilian children with NF1 to primarily evaluate head size, stature, birth weight and weight. The study had a number of limitations including small sample sizes and retrospective analyses. The FDA contends that reliable conclusions regarding selumetinib's effect on weight in the pediatric study population cannot be made based on the available data. This potential safety signal could be addressed with longer term follow-up of patients in the post-marketing phase.

The FDA additionally notes that the Rockwell 2001 reference listed in the Applicant's position statement is an error. The reference should be (Ribeiro and Coutinho 2015).

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The FDA's Assessment:

Refer to Section 8.1.2.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

See the Applicant's Position below.

The Applicant's Position:

Intrinsic Factors

There were no clinically meaningful differences in the safety profile of selumetinib with respect to age, gender and race in the Pediatric Pool. Though some differences were observed, it is difficult to draw conclusions based on the small number of pediatric patients in the analysis (N=74) and the disproportionate impact of the difference of a few patients between subgroups.

No dose adjustment for any patient subgroup is considered necessary, and therefore not recommended in the proposed labelling. Evaluation of these safety data did not indicate the need for any additional safety monitoring over that already outlined in the proposed labelling as part of routine risk minimization.

Effect of Age

An evaluation of AEs, AEs of CTCAE Grade 3 or higher, SAEs, AEs of special interest, suggested that there were some differences between pre-pubertal patients (≥ 2 to 11 years of age) and post-pubertal patients (12 to 16 years of age) in the Pediatric pool. Dry skin and pyrexia were more prevalent in children ≥ 2 to 11 years; dermatitis acneiform occurred at a higher frequency in the 12 to 16 years age group. However, these findings were not considered clinically significant, nor do they represent a pattern and may be likely caused by variability within a small single-arm study.

In the Adult monotherapy pool, although the incidence of SAEs was higher in the older population (≥ 65 years of age), there were no differences in incidence of $>10\%$ for any individual AE.

In population PK analysis, based on BSA derived dosing, there was no clinically relevant difference in exposure of selumetinib due to patients' age.

Effect of Gender

An evaluation of AEs, AEs of CTCAE Grade 3 or higher, SAEs, AEs of special interest, suggested that there were some differences between male and female patients in the Pediatric pool; AEs of anaemia, hypertension and sinus tachycardia were reported at a 2-fold higher frequency in male patients whereas AEs of alopecia (reported term: hair thinning) and hair colour changes were reported at a 2-fold higher frequency in female patients.

Based on population PK analysis, gender has no clinically relevant impact on selumetinib exposure.

Effect of Race

In both the Pediatric pool and the Adult monotherapy pool, the number of patients in the non-White group was too small to allow a reliable comparison and evaluation of any meaningful differences with the White group.

Increased systemic exposure (approximately 1.5 to 2-fold) has been observed in adult healthy volunteers of Asian subjects, although there is considerable overlap in the range of exposure experienced for both Asian and Western subjects when corrected for body weight. It is anticipated that the observed PK ethnic differences of selumetinib are likely not to be of clinical relevance, particularly as pediatric patients will follow a selumetinib dosing regimen based on BSA (see Section 6.3.1). (b) (4)

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of safety subgroup analyses for age, gender, and race in the pediatric pool and emphasizes the limited sample sizes for these analyses. Please refer to Section 6.2.2.2 for a discussion of age and gender effects on PK exposures.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

With respect to the provision of long-term safety-data, there will be continued safety monitoring of patients in SPRINT Phase II Stratum 1.

The FDA's Assessment:

See Section 8.2.10.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

See the Applicant's Position below.

The Applicant's Position:

No human carcinogenicity data are available. Based on pre-clinical studies selumetinib is not considered carcinogenic (see Section 5.5.3) and the number of patients on SPRINT who

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developed MPNST does not exceed the known background incidence of malignant transformation of PN to MPNST in NF1 population.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Human Reproduction and Pregnancy

Data:

See the Applicant's Position below.

The Applicant's Position:

Based on nonclinical data (Section 5.5.4), it is recommended that a pregnancy test should be performed on female patients of child bearing potential prior to treatment with selumetinib. In addition, female patients of child bearing potential must use adequate contraception during treatment and for at least 1 week after completion of treatment. Lactating mothers should be advised not to breast-feed during treatment with selumetinib. Male patients with sexual partners who are pregnant or who could become pregnant (ie, females of child bearing potential) should use acceptable methods of contraception for at least 1 week after completing treatment with selumetinib to avoid pregnancy and/or potential adverse effects on the developing embryo. Acceptable methods of contraception include implants, injectables, combined oral contraceptives (which must all be combined with barrier methods of contraception as any interaction with selumetinib is unknown), some IUDs and vasectomized partner. Sexual abstinence is also an acceptable method of contraception according to ICHM3.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

Data:

See the Applicant's Position below.

The Applicant's Position:

Given that the NDA is for a pediatric indication, Section 8.2.4 provides substantial safety information for this patient population.

With respect to effects on developing organ systems, microscopic findings consistent with physeal dysplasia were observed in the femora-tibial joint in rats. These effects were observed at exposure multiples 11-fold greater than the free exposure levels in humans. Physeal dysplasia has not been observed in monkeys or mice treated with selumetinib for periods of up to 6 months, the latter which were of an age and immaturity to have had open growth plates. A juvenile toxicity study is not considered likely to add further to the risk assessment for this finding. As a result of these nonclinical findings, physeal dysplasia has been prospectively identified as an AESI. Pediatric patients have been monitored for signs of physeal dysplasia and bone growth effects. To date no significant changes in these parameters have been reported in pediatric patients following treatment with selumetinib.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Growth and development parameters will continue to be assessed as part of the SPRINT protocol's long-term safety follow-up. See Section 8.2.10.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Not applicable.

The Applicant's Position:

Overdose

Inadvertent misdosing of selumetinib, such as administration of a higher selumetinib dose than stated in the protocol, should be followed up and treated with appropriate supportive care until recovery. Selumetinib overdose is defined as any dose received above 25 mg/m². There is no specific treatment for overdose. Due to low elimination of selumetinib related material in urine, dialysis is unlikely to influence the elimination during overdose. Physicians should follow general supportive measures and should treat the patient symptomatically.

Drug Abuse

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

Withdrawal and Rebound

In SPRINT, all patients are mandated to complete a safety visit approximately 30 days following the last dose of selumetinib. Based on the available data, no evidence of withdrawal or rebound effects was noted following discontinuation of treatment with selumetinib therapy.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

This sub-section is not applicable as selumetinib is not currently registered (or approved) in the US or in any other part of the world.

The FDA's Assessment:

Not applicable.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

AstraZeneca has comprehensive processes for signal detection, regular safety reviews, identifying and evaluating issues potentially affecting patient safety, and developing safety recommendations (including changes to the reference safety information). In addition, these processes enable the identification of safety topics that need to be kept under close surveillance. The safety signal detection activities include review of reported AEs from post marketed sources, and a review of the published literature relevant to selumetinib. The post market data for selumetinib will be regularly reviewed for new findings or trends.

In addition to routine pharmacovigilance, the following post-authorization measures are planned for selumetinib in the treatment of patients with NF1 and PNs:

- Long term safety follow-up from the SPRINT Phase II Stratum 1 study.

SPRINT: Planned Long Term Follow-up

The CSP for the SPRINT study (version in place at the DCO date, following Amendment M; dated 28 September 2016) for Phase II Stratum 1 has a primary objective to evaluate the confirmed

PR and CR rate of selumetinib in children and young adults with NF1 PN using volumetric MRI analysis. The primary analysis has been conducted after all patients with a confirmed response had been followed-up for at least 12 months from the onset of response.

At the DCO for the primary analysis (29 June 2018), 50 patients in SPRINT Phase II Stratum 1 had received selumetinib treatment for a median total duration of 802 days (approximately 26 months; range 28 days [approximately 1 month] to 1053 days [approximately 35 months/3 years]). The median actual durations were similar which shows that most patients were able to receive assigned treatment and that the duration of any treatment interruptions were usually short. Of the 50 patients in SPRINT Phase II Stratum 1, 34 patients remain on selumetinib treatment. At the same DCO date, 24 patients in SPRINT Phase I had received selumetinib treatment for a median total duration of 1606 days/53 treatment cycles (approximately 53 months/4.4 years; range: 158 days [approximately 5 months] to 2169 days [approximately 71 months/5.9 years]). Of these 24 patients, 13 patients remain on selumetinib treatment.

Safety data will continue to be reported: AstraZeneca employs routine pharmacovigilance activities which are designed to proactively identify and/or characterize safety concerns of selumetinib and will inform risk mitigation strategies for the important identified risks. These activities include coordination with the study sponsor for ongoing receipt and analysis of AE data from SPRINT.

The long duration of selumetinib exposure in SPRINT did not affect the ability of the patients to remain on treatment and the fact that AEs have been managed by dose modifications over this long duration provides valuable evidence in support of tolerability and safety of selumetinib in long term use. Per protocol, all patients in Phase II Stratum 1 will enter long-term follow-up for a duration of 7 years from the initiation of treatment or 5 years after completion of selumetinib, whichever takes longer. If a patient is no longer on treatment but remains on the study, during long term follow-up, these patients will have annual visits where a complete physical examination will be conducted (including assessment of height, weight, BSA, and performance status), together with: a complete blood count; a differential platelet count; serum electrolytes; renal and liver function tests; CPK level; and urinalysis assessment. Additionally, ophthalmology examinations and echocardiography will be performed if clinically indicated.

The follow-up assessments will note whether there have been any significant medical issues in the preceding 12 months with a focus on possible AEs related to selumetinib and safety follow-up will specifically collect data on whether patients have seen a pediatric oncologist in the past year (with reasons why, if the answer is affirmative). Moreover, for patients who remain on selumetinib treatment, all of the above safety assessments will be carried out as per the following schedule: prior to Cycles 2 to 5, then every other cycle (prior to Cycles 7, 9, 11,

13); then every 4 cycles (prior to Cycles 17, 21, 25); then every 6 cycles (prior to Cycles 31, 37, 43, etc.).

As part of the long-term follow-up of the SPRINT study, all SAEs (including SUSARs) that occur following database lock are reported to the AstraZeneca Patient Safety Department by NCI/CTEP; all SAEs are followed-up as necessary. In addition, a line listing of all AEs occurring in SPRINT will be provided to the AstraZeneca Patient Safety Department on a quarterly basis for inclusion in safety surveillance. The line listing of AEs will be analyzed by AstraZeneca to provide information regarding signal evaluation and evaluation of risks and new information as applicable will be analyzed and presented in the Periodic Safety Update Report. In addition, and in accordance with NCI standard AE reporting procedures, any AE which has a change in CTCAE grade is reported as a separate AE.

The FDA's Assessment:

The FDA agrees with the long-term follow-up safety monitoring that is part of the SPRINT protocol. See Section 13 for additional clinical safety post-marketing requirements (PMRs).

8.2.11. Integrated Assessment of Safety

Data:

See the Applicant's Position below.

The Applicant's Position:

The safety profile of selumetinib 25 mg/m² BID (approximately every 12 hours) in SPRINT Phase II Stratum 1, is consistent with the well characterized safety profile of selumetinib (20 to 30 mg/m² BID) in 74 pediatric patients with NF1 and inoperable PN and with the known safety profile in the MEK drug class. These safety findings are supported by data from 347 adult patients with cancer who received selumetinib 75 mg BID.

- Overall the safety profile for selumetinib as treatment for pediatric patients aged 3 to 18 years and above with NF1 and symptomatic, inoperable PN, including commonly reported events is considered manageable, acceptable and well tolerated.
- Overall, the type of AEs reported were consistent with the safety profile for the MEK inhibitor class of drugs. The safety profile of selumetinib with respect to the frequency and CTCAE severity of AEs in the SPRINT Phase II Stratum 1 pediatric population was consistent to that observed in the adult populations.
- The majority of AEs reported with selumetinib were manageable with either selumetinib dose modifications and/or supportive therapy. Most resolved during the course of the study and generally did not affect the ability of patients to remain on treatment for long periods of time.
- The frequently observed AEs (>45%) that characterize the selumetinib safety profile (acneiform rashes, gastrointestinal events [diarrhoea, nausea and vomiting], paronychia,

and pyrexia, AST increased, and fatigue/asthenia) did not generally lead to discontinuation of selumetinib in pediatric patients

- Considering the prolonged duration of exposure, the incidence of treatment-related SAEs (12.0%) and treatment-related permanent discontinuation of selumetinib treatment (12.0%) in SPRINT Phase II Stratum 1, with similar incidences seen in the Pediatric pool, supports a well-tolerated safety profile. No deaths were reported on this study.
- AEs of CTCAE Grade ≥ 3 , by PT ($\geq 5\%$) in SPRINT Phase II Stratum 1 were diarrhoea, hypoxia, pyrexia, blood CPK increased, paronychia, vomiting, and weight increased. A similar profile was seen in the Pediatric pool.
- The AESIs noted in the Pediatric pool are consistent with those seen in the Adult monotherapy pool. No new significant safety concerns were identified.
- No evidence of the retinal events of csr/RPED or RVO, or events suggestive of physeal dysplasia associated with selumetinib have been identified in the context of considerable duration of exposure in pediatric patients.

The majority of the causally attributed AEs appear to occur in the first year of selumetinib treatment. The safety profile of selumetinib does not appear to significantly worsen over time. Pediatric specific AE management guidelines are in place to ensure consistency in AE management. Long term safety will be continually assessed as part of routine pharmacovigilance.

The FDA's Assessment:

The FDA generally agrees with the Applicant's integrated assessment of safety except the statement that the frequency and severity of AEs in the pediatric population was similar to the adult population.

The pediatric safety data from SPRINT, the supportive adult monotherapy pooled data, the supplemental data from the selumetinib expanded access program and externally-sponsored pediatric selumetinib studies, and the additional safety analyses of the Applicant's global selumetinib database submitted during the review allowed for an informed risk assessment of selumetinib in the intended NF1 PN population.

The primary safety data was from the NCI SPRINT trial, an open-label, multicenter, single arm trial in 74 patients 3 to 18 years of age with NF1 and inoperable PN. Although the sample size was relatively small, the median duration of treatment was approximately 2 years, permitting a reasonable evaluation of risk for cumulative toxicities with chronic dosing.

There were no fatal AEs in SPRINT. SAEs occurred in 23% of patients including 11% who experienced selumetinib-related SAES. AEs leading to permanent discontinuation occurred in 12%, and approximately one third of patients required dose reduction for an AE. Grade 3-4 AEs occurred in 68% of patients including 43% of patients who experienced Grade 3-4 AEs

considered at least possibly related to selumetinib. The most common AEs (more than 30% of patients) in the pediatric pool included vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, musculoskeletal pain, fatigue, pyrexia, dermatitis acneiform, stomatitis, headache, oropharyngeal pain, paronychia, pruritus, cough, dermatitis, constipation, nasal congestion, hair disorder, influenza like illness, and allergic rhinitis. Given the relatively low discontinuation rate over a fairly long treatment duration, it appears that AEs were tolerable and manageable with dose modifications and supportive care in pediatric patients treated with selumetinib.

Important risks of selumetinib are similar to those of other MEK inhibitors including ocular, cardiac, musculoskeletal, GI and dermatologic toxicities. Some rare, but serious, class-related safety signals (e.g., RVO, RPED, rhabdomyolysis, PPES) were not identified in the SPRINT pediatric data. Supportive adult data and additional pediatric data from the selumetinib expanded access program for PN and from externally-sponsored pediatric trials provided a larger sample size to evaluate less common adverse reactions. The review of these additional data sources suggests that selumetinib has a similar safety profile to commercially approved MEK inhibitors. The pediatric PN population under the labeled indication likely has similar risk for developing these class-related toxicities, and the product label attempts to mitigate this risk by including relevant warnings, precautions and dose modification guidelines.

As part of the overall risk assessment, the FDA additionally considered the benign nature of the NF1 PN indication and the intention for chronic dosing of selumetinib in pediatric patients. The recommended indication is restricted to patients with inoperable PN that is symptomatic. The patients in SPRINT had substantial PN-related morbidity and had long treatment durations with a low discontinuation rate suggesting that selumetinib at the recommended dose was reasonably safe and tolerable. The longer term safety profile of selumetinib for chronic dosing in a pediatric population will be further assessed through post-marketing requirements.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

While there were no major statistical issues with this application, there are some limitations to deriving inference from a small, non-randomized study. The response rate of patients treated with selumetinib varied by assessor (NCI central review vs. independent central review); however, regardless of assessor, the estimated response rate was considered clinically and statistically meaningful. Additionally, the responses are durable, but the study follow-up was not sufficiently mature to characterize median duration of response. Results for any other endpoints in the SPRINT Phase II Stratum 1 trial are considered descriptive.

FDA considered the comparisons of efficacy endpoints in SPRINT Phase II Stratum 1 to the placebo arm of Study 01-C-0222 or the Natural History study to be exploratory, due to potential

between-study differences including patient eligibility criteria, assessment frequencies of endpoint, and endpoint definition. Furthermore, the lack of covariate information available for these external data limited the ability to compare data sources or to adjust for potential confounding or bias, and so the results of any comparisons are not interpretable.

8.4. Conclusions and Recommendations

The FDA's Assessment:

NF1 PN is a rare, benign tumor that can cause substantial morbidity for patients starting at a young age. Surgical intervention is common and typically based on progressive PN-related symptoms or functional impairment because it is rarely curative and regrowth is common. There are currently no FDA-approved systemic therapies for treatment of PN. The absence of functional neurofibromin and the resulting upregulation of RAS signaling of the RAF/MEK/ERK pathway in patients with NF1 provides a sound biologic rationale for MEK inhibition as a treatment approach for NF1 related tumors, including PN.

The clinical benefit of selumetinib for pediatric patients with inoperable and symptomatic NF1 PN is based on the results of the NCI SPRINT trial. Efficacy results from SPRINT Phase II Stratum 1 demonstrated a confirmed ORR per REiNS criteria of 66% (95% CI: 51, 79) based upon NCI central review and 44% (95% CI: 30, 59) based upon independent central review (ICR). Among the 33 responding patients included in the NCI assessment, the median DOR was not reached and 82% had a DOR of at least 12 months. The observed ORRs in SPRINT Phase 1 [67% (95% CI: 45, 84)] and SPRINT Phase II Stratum 2 [68% (95% CI: 47, 85)] were consistent with the primary Phase II Stratum 1 results and similarly durable. Additionally, a natural history study of NF1 conducted by the NCI Pediatric Oncology Branch (POB) and submitted as part of the application demonstrated that a key characteristic of NF1 PN is the uncommon occurrence of spontaneous regression such that the observed tumor responses in SPRINT can be concluded to be the effect of selumetinib.

Clinical outcomes data were considered essential for demonstrating the clinical benefit of selumetinib, given the benign, albeit morbid, nature of NF1 PN. The SPRINT trial evaluated selumetinib effects on PN-related functional impairment, symptoms, and disfigurement via various COA measures and photographic evaluations that were conducted with scheduled tumor response assessments. Acknowledging the limitations of the single arm trial design and the relatively small sample sizes available for analysis of specific morbidities, the FDA observed a general trend toward an association between reduction in tumor volume and durable improvement in clinical outcomes during SPRINT Phase II Stratum 1.

The primary safety risks of selumetinib are consistent with the profiles of other approved MEK inhibitors. ADRs in pediatric patients receiving selumetinib were frequent and varied; however, most were low-grade and manageable with dose interruptions, reductions and supportive care. Selumetinib appears to be tolerable in patients with NF1 PN given the relatively low incidence

of SAEs in the context of a long duration of exposure for the patients who were treated in SPRINT. However, there is no evidence that pediatric patients are at less risk for uncommon, but serious, MEK class toxicity effects that were not identified in the pediatric pool; therefore, specific safety precautions, dose-modifications, and management guidelines are included in product labeling, and the marketing approval includes post-marketing requirements for long-term safety evaluations in pediatric patients.

In conclusion, the benefit:risk assessment for selumetinib is favorable, and the FDA review team recommends regular approval for selumetinib for the treatment of pediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN at a dose of 25 mg/m² administered twice daily on a continuous basis. Selumetinib has demonstrated statistically significant and clinically meaningful efficacy, including confirmed ORR that is durable and correlates with improvements in PN-related clinical morbidities. These results represent direct clinical benefit for pediatric patients with NF1 PN. The safety profile of selumetinib is consistent with other MEK inhibitors and is acceptable in view of the serious nature of inoperable PN.

The clinical reviewers do not recommend a REMS be implemented for selumetinib given the current safety profile and the experience of the medical community in managing expected MEK inhibitor ADRs. Long-term monitoring will be conducted via PMRs for safety, growth and development given the intended chronic use for pediatric patients. Risk management based on labeling and routine and enhanced pharmacovigilance will be employed to ensure the safe and effective use of selumetinib in patients with NF1 PN.

Arup Sinha, Ph.D.
Primary Statistical Reviewer

Pallavi Mishra-Kalyani, Ph.D.
Statistical Team Leader

Denise Casey, M.D
Primary Clinical Reviewer

Suzanne Demko, P.A.-C.
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) or Special Government Employees (SGEs) for this NDA. There were no controversial issues that would benefit from advisory committee discussion.

10 Pediatrics

The Applicant's Position:

Not applicable. This NDA is for a pediatric indication. Additionally, selumetinib has been granted Orphan Drug Designation for the treatment of NF1, thereby exempting from Pediatric Research Equity Act requirements.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

11 Labeling Recommendations

The table below (Table 58) summarizes changes to the proposed prescribing information (PI) made by the FDA. See the final approved prescribing information for KOSELUGO (selumetinib) accompanying the approval letter for more information.

Table 58 Highlights of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Full Prescribing Information		
Indications and Usage	Limited the application to pediatric patients 3 years of age and older.	Expanded the indication to pediatric patients 2 years and older, because the safety, effectiveness and pharmacokinetics of selumetinib in pediatric patients 2 years of age will likely be similar to that of pediatric patients 3 years of age and older.
Dosage and Administration, Recommended Dosage	Included a statement (b) (4) in patients with a BSA less than 0.55 m ² ; this proposal implies a concern with safety or effectiveness. Recommended (b) (4) for patients with a BSA of 0.55 – 0.69 m ²	Revised to state that a recommended dosage for patients with a BSA less than 0.55 m ² has not been established. Revised recommended dosage to 20 mg in the morning and 10 mg in the evening to retain similar exposure as compared to that achieved for other BSA subgroups with the proposed dosages. Added that this product should not be administered to patients unable to swallow a whole capsule.
Dosage and Administration, Dosage Modifications for Adverse Reactions	For patients with a BSA of 0.55 – 0.69 m ² , proposed (b) (4) Provided a table (b) (4)	Revised to 10 mg twice daily for the first dose reduction and 10 mg once daily for the second dose reduction based on changes made to the recommended dosage for this subgroup. Created a two column table that includes dosage modifications for left ventricular dysfunction, ocular toxicity, gastrointestinal toxicity, increased CPK, skin toxicity and other adverse reactions. Based the recommended dosage modifications on the SPRINT

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		protocol.
Dosage and Administration, Dosage Modifications for Drug Interactions	...	Added a new subsection to describe recommended dosage modifications for strong or moderate CYP3A4 inhibitors and fluconazole based on clinical drug interaction studies and model-informed approaches.
Warnings and Precautions	Included Warnings and Precautions for (b) (4)	Revised Warnings and Precautions to include subsection describing cardiomyopathy, ocular toxicity, gastrointestinal toxicity, skin toxicity, increased CPK, increased levels of vitamin E and risk of bleeding, and embryo-fetal toxicity. Based revisions on findings from clinical studies in adults and pediatric patients who received selumetinib in SPRINT and other clinical trials across a range of tumors, observed adverse reactions with other drugs substances that inhibit MEK, animal findings, published literature, drug product and mechanism of action.
Adverse Reactions, Clinical Trials Experience	... Included a table describing adverse reactions that occurred (b) (4) (b) (4)	Added a description of the safety populations included in the W&P. Added description of key eligibility criteria that could affect evaluation of safety data; exposure at 12 months or longer and greater than 2 years; serious adverse reactions; adverse reactions that led to permanent discontinuation, dosage interruptions, dose reductions; and most common adverse reactions. Expanded table to describe adverse reactions that occurred in 20% or more of patients. Listed the adverse reactions in decreasing order within a category and the categories in decreasing order based on the highest incidence for a single adverse reaction in that category. Expanded list of less common adverse reactions to include adverse reactions that occurred in less than 20% of patients based on changes made to the table.

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	...	Revised table describing laboratory abnormalities to include laboratory abnormalities documented in the laboratory dataset that worsened by at least one grade in 15% or more of patients. Calculated rates based on the number of patients who had a baseline result and at least one on-study laboratory test.
Use in Specific Populations, Pregnancy and Lactation and other subsections	Included exposure multiples based on AUC calculated using (b) (4)	Revised exposure multiples based on AUC calculated using total concentrations.
(b) (4)		
Clinical Pharmacology	...	Included a statement describing the exposure-response relationship, the content of a high- and low-fat meal, and the effects of race and ethnicity on the pharmacokinetics of selumetinib. Limited the description of the pharmacokinetics of selumetinib in adults, because labeling must not imply or suggest an indication not listed in Indications and Usage [21 CFR 201.57 (c)(2)(iv)]
Clinical Studies	...	Described efficacy results by NCI assessment in table and investigator assessment below table. See discussion under section 8.1.2 of this review. Removed (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The label includes listings of important adverse reactions that have been observed across the MEK inhibitor class as well as dose modifications and management guidelines for these events. Prescribers are increasingly experienced with monitoring and treating expected MEK inhibitor safety effects given recent approvals of this drug class, and oncologists are generally experienced in the monitoring and management of serious risks.

The FDA does not recommend a REMS be implemented for selumetinib given the current safety profile and the experience of the medical community in managing expected MEK inhibitor related ADRs.

A plan for enhanced pharmacovigilance is include as part of postmarketing requirements for selumetinib, as follows:

“For a period of 5 years from the U.S. approval date, submit all cases reported of adverse events of special interest (AESIs), including ocular toxicity events including but not limited to retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), cardiac toxicity events (including but not limited to ventricular dysfunction), muscle toxicity events (including but not limited to rhabdomyolysis), gastrointestinal toxicity events (including but not limited to colitis, ileus, intestinal obstruction, and intestinal perforation) with serious outcomes in pediatric patients receiving Koselugo® (selumetinib) for the treatment of NF-1 as 15-day Alert reports [as described under 21 CFR 314.80(c)(1)], and provide detailed analyses of these AESIs reported from clinical study, and post-marketing reports in your periodic safety report [i.e., the Periodic Adverse Drug Experience Report (PADDER) required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report (PBRER) format]. These analyses should show cumulative data relative to the date of approval of Koselugo® (selumetinib) as well as relative to prior periodic safety reports. These analyses should include case narratives, with the following information in a table format: demographics, predisposing risk factors/comorbidities, signs, symptoms and relevant laboratory data leading to diagnosis, rechallenge/dechallenge information. Medical literature reviews for case reports/case series of these AESIs reported with Koselugo® (selumetinib) should also be provided in the periodic safety report.”

The applicant has agreed to provide the information requested for the time requested in a document submitted by email on March 13, 2020, with a plan for an official submission to the NDA on March 17, 2020.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following postmarketing requirements, reviewed and agreed to by the Applicant, will be included in the action letter for this NDA:

FDA PMR #1

Characterize and evaluate the long-term safety effects and any potential for serious adverse risks of selumetinib on the growth and development of pediatric patients. Submit the complete final report and long-term follow-up data from pediatric patients enrolled on SPRINT and ongoing or completed studies of selumetinib.

All patients must be evaluated for growth and development milestones annually for at least 7 years from initiation of selumetinib. Evaluations must include: growth as measured by weight, height, height velocity, height standard deviation scores (SDS), age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression. Descriptive statistics (including mean and standard deviation values) of on-study data for growth velocity must be presented. Growth velocity during the trial should be compared with growth velocity at baseline (if pre-baseline data are available). Provide analyses of height and weight data that assess measures of central tendency and outlier analyses using height and weight z-scores.

PMR Schedule Milestones

Trial Completion: September 2025

Final Report Submission: March 2026

FDA PMR #2

Characterize and evaluate the long-term safety effects and any potential for specific serious adverse risks of selumetinib in pediatric patients. Submit the complete final report and long-term follow-up safety data (minimum of 7 years) from pediatric patients enrolled on SPRINT and all other ongoing or completed studies of selumetinib to include an analysis of the following toxicities in pediatric patients: ocular toxicity (including but not limited to retinal pigment epithelial detachment and retinal vein occlusion), cardiac toxicity (including but not limited to ventricular dysfunction), muscle toxicity (including but not limited to rhabdomyolysis and symptomatic and asymptomatic CPK elevation), serious gastrointestinal toxicity (including but not limited to colitis, ileus, intestinal obstruction, and intestinal perforation), and serious dermatologic toxicity.

PMR Schedule Milestones

Trial Completion: September 2025

Final Report Submission: March 2026

FDA PMR #3

Submit the final report and datasets from a pharmacokinetic trial in pediatric patients to confirm the effect of a low-fat meal on selumetinib exposure with the marketed capsule formulation and evaluate whether administration of selumetinib with food may alleviate gastrointestinal toxicities. Confirm appropriate dosing recommendation of selumetinib with a low-fat meal that maintains efficacy with acceptable safety.

PMR Schedule Milestones

Draft Protocol Submission: September 2020

Final Protocol Submission: December 2020

Trial Completion: October 2022

Final Report Submission: April 2023

14 Division Director (DHOT) (NME ONLY)

John Leighton, Ph.D.

X

15 Division Director (OCP)

Nam Atiqur Rahman, Ph.D.

X

16 Acting Deputy Division Director (OB)

Yuan-Li Shen, Ph.D.

X

17 Division Director (Clinical)

Harpreet Singh, M.D.

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Marc Theoret, M.D.

X

19 Appendices

19.1. References

The Applicant's References:

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NDA Multi-disciplinary Review and Evaluation NDA 213756
Koselugo (selumetinib)

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The FDA's References:

FDA's references are imbedded above (and shaded) for the ease of the reader.

19.2. Financial Disclosure

The Applicant's Position:

Per CTEP policy, CTEP does not provide Financial Disclosure Forms to external parties.

CTEP queried investigators for possible financial conflict of interest with AstraZeneca and Merck for NCI Protocol 8799. There were zero investigators who reported a possible financial conflict of interest with AstraZeneca or Merck according to information submitted to CTEP.

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Financial Disclosure Forms will be provided directly to Regulatory Authorities upon their request.

The FDA's Assessment:

Covered Clinical Study (Name and/or Number): SPRINT (NCI Protocol 8799)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>75</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>3</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes. Plasma and urine concentrations of the active parent drug selumetinib and its active N-desmethyl metabolite were measured in the clinical pharmacology and biopharmaceutics studies.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma concentrations of selumetinib and its N-desmethyl metabolite were measured in all studies. The unbound plasma concentration of selumetinib was measured in both the hepatic impairment study (D153200082) and renal impairment study (D1532C00081). In both of the organ impairment studies, a validated LC-MS/MS analytical method was available for measuring the concentration of unbound moieties in human plasma ultrafiltrate to evaluate protein binding. In the renal impairment study, plasma protein binding in the ESRD group (99.4%) was ~35% lower than patients with normal renal function (99.6%). In the hepatic impairment study, the fraction unbound for selumetinib was similar in normal, mild, and moderate groups: 0.00343, 0.00277, 0.00295, respectively, while the severe hepatic impairment group had a higher unbound ratio of 0.00691.

What bioanalytical methods are used to assess concentrations?

Bioanalytical methods in human matrices for the determination of selumetinib (AZD6244, AR142886) and its active N-desmethyl metabolite were initially developed and validated on behalf of Array Biopharma (Colorado USA) and AstraZeneca at [REDACTED] (b) (4)

[REDACTED] Table 59 summarizes the bioanalytical methods validated and used to quantify selumetinib and its N-desmethyl metabolite. Overall, the precision, accuracy, selectivity and performance of the methods used to analyze selumetinib and metabolite in plasma, plasma ultrafiltrate, and urine were acceptable. See Table 60 below for accuracy and precision summary data and additional stability data for the two analytes.

Table 57 Bioanalytical methods for selumetinib and N-desmethyl selumetinib in human biological samples

Method	Analyte	Matrix (assay volume)	Report No ^a	LLOQ ng/mL	Linear range ng/mL (weighting)
WMTD070	Selumetinib	EDTA	(b) (4) 100362,	2.00	2-2000 (1/x ²)
	N-desmethyl selumetinib	plasma (25 µL)	(b) (4) 101034 and 100363	2.00	2-500 (1/x ²)
WMTD133	Selumetinib	EDTA	(b) (4) 101378	2.00	2-2000 (1/x ²)
	N-desmethyl selumetinib	plasma (25 µL)		2.00	2-500 (1/x ²)
244HPP	Selumetinib	EDTA	8260247	2.00	2.00-2000 (1/x ²)
	N-desmethyl selumetinib	plasma (25 µL)		2.00	2.00-500 (1/x ²)
ANAHPP	Selumetinib	EDTA	8277095	2.00	2.00-2000 (1/x)
	N-desmethyl selumetinib	plasma (50 µL)		2.00	2.00-500 (1/x)
AZPUFP	Selumetinib	EDTA	8297322	5.00	5.00-5000 (1/x ²)
	N-desmethyl selumetinib	plasma ultra-filtrate ^b (50 µL)		1.00	1.00-1250 (1/x ²)
AZ6PUFP	Selumetinib	EDTA	8307806	0.500	0.500-250 (1/x ²)
	N-desmethyl selumetinib	plasma ultrafiltrate ^b (50 µL)		0.500	0.500-250 (1/x ²)
244HUP	Selumetinib	Urine ^b	8297321	10.0	10-10000 (1/x ²)
	N-desmethyl selumetinib	(50 µL)		2.00	2-2500 (1/x ²)
AZ6HDP	Selumetinib	Dialysate ^b	8298084	1.00	1.00-1000 (1/x ²)
	N-desmethyl selumetinib	(300 µL)		0.200	0.200-250 (1/x ²)

^a Refers to Method Validation Report, located in Module 5.3.1.4.1.

^b Actual matrix includes 0.1% Triton X-100.

EDTA ethylenediaminetetraacetic acid; LLOQ Lower Limit of Quantification.

Source: GSR 2.7.1 summary of biopharmaceutical studies and associated analytical methods.

Table 60 Validation accuracy and precision summary data and additional stability data for bioanalytical methods for selumetinib and N-desmethyl selumetinib in human plasma samples

	Analyte	Method WMTD070	Method WMTD133	Method ANAHPP	Method 244HPP
Between-run accuracy (%)	Selumetinib	93.5–105.5 ^a , 94.7–102.5 ^b	96.0–104.2	92.7–100.0	99.5–105.0
	N-desmethyl selumetinib	93.6–105.5 ^a , 99.8–103.5 ^b	98.0–103.0	98.3–103.5	95.5–98.3
Between-run precision (%)	Selumetinib	3.9–10.3 ^a , 1.4–7.1 ^b	3.4–8.7	5.1–7.0	2.7–12.5
	N-desmethyl selumetinib	3.7–12.1 ^a , 1.7–11.1 ^b	5.0–10.8	3.2–10.1	3.8–11.2
Within-run accuracy (%)	Selumetinib	90.9–109.5 ^a , 88.0–103.0 ^b	94.0–108.7	89.3–98.8	96.5–107.3
	N-desmethyl selumetinib	88.7–113.0 ^a , 87.7–111.1 ^b	95.1–111.3	93.1–112.0	92.5–100.5
Within-run precision (%)	Selumetinib	1.0–13.2 ^a , 1.2–11.8 ^b	1.5–10.6	1.5–8.6	0.8–18.4
	N-desmethyl selumetinib	0.8–14.4 ^a , 1.0–2.4 ^b	2.8–13.6	1.4–11.8	1.8–14.9
Stability in whole blood ^c :	Selumetinib			2 hours	
	N-desmethyl selumetinib				
Plasma stability on wet ice:	Selumetinib			at least 6 hours	24 hours (at room temp)
	N-desmethyl selumetinib				
Processed sample stability/viability ^d :	Selumetinib	NA/3 days (36 hours at room temp)	NA/ 4 days (5 days at room temp)	at least 96/177 hours	115 hours stability
	N-desmethyl selumetinib				
Freeze/thaw cycle stability (-10°C to -30°C and -60°C to -80°C)	Selumetinib			at least 5 cycles	
	N-desmethyl selumetinib				
Long term stability acceptable up to ^e :	Selumetinib	24 months (and at -20°C)			
	N-desmethyl selumetinib	9 months (and at -20°C)			

^a Report reference (b) (4), 00362.

^b Report reference (b) (4), 101227.

^c At 37°C left to cool at room temperature and on wet ice under white or yellow light.

^d At 2 to 8°C.

^e At a nominal -80°C (report references (b) (4), 04081/1, (b) (4), 101034, 8260247).

Source: GSR 2.7.1 summary of biopharmaceutical studies and associated analytical methods.

19.4.2. PK and PD Assessments

Clinical Pharmacokinetics

The clinical PK of selumetinib and its N-desmethyl metabolite in pediatric patients with NF1 and inoperable PN who were 3 to 18 years old at enrollment was evaluated in the SPRINT study. The SPRINT study included Phase I dose identification across 3 doses levels 20, 25 and 30 mg/m² in 24 pediatric patients, and Phase 2 pivotal trial in 50 pediatric patients at dose level 25 mg/m². Blue capsules (25 mg dose strength) in combination with white capsules (10 mg dose strength) were used to make up to the nearest BSA-based dose. Table 61 and Table 62 represent selumetinib and its N-desmethyl metabolite PK parameters in pediatric patients after single dose.

Table 61 Selumetinib PK parameters in pediatric patients after single dose

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

^a Geometric mean. GCV% geometric coefficient of variation

^b Median (range)

^c Arithmetic mean (SD)

^d AUC₀₋₁₂

Source: Table 11.2.3.2.1, SPRINT Phase I CSR; Table 11.2.5.2.2, SPRINT Phase II CSR.

Table 62 N-desmethyl selumetinib metabolite PK parameters in pediatric patients after single dose

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

Source: Table 11.2.3.2.3, SPRINT Phase I CSR; Table 11.2.5.2.3, SPRINT Phase II CSR.

Selumetinib PK is also characterized in healthy adult subjects taking single oral dose with regard to absorption, distribution, metabolism and elimination (ADME) properties, food interactions, drug interactions, effect on QT, ethnicity, renal and hepatic impairment. The PK and relative BA of selumetinib were also studied in adult patients with advanced malignancies (Study 05). Table 60 and Table 61 shows the PK of selumetinib and its N-desmethyl metabolite in healthy subjects and adult patients after single dose. Results showed a similar ADME between adult patients/HV and pediatric patients for both parent drug and the active metabolite.

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Table 58 Selumetinib PK parameters in healthy subjects and adult patients after single dose

Adult patients with solid tumours (Study 05)							
Dose (mg)	N	C _{max} (ng/mL) (GCV%) ^a	t _{max} (h) (Range) ^b	AUC (ng [*] h/mL) (GCV%) ^a	CL/F (L/h) (SD) ^c	V _{ss} /F (L) (SD) ^c	t _{1/2} (h) (SD) ^c
25 white capsule	6	369 (28)	1.3 (1-2)	1361 (23)	18.8 (4.1)	126 (54.2)	7.0 (1.2)
50 white capsule	7	1036 (52)	1 (0.5-1.5)	3075 (53)	18.0 (8.8)	125 (59.1)	7.2 (2.1)
75 white capsule	7	1207 (48)	1.5 (1-2)	6335 (26)	12.1 (2.9)	89 (32.8)	5.3 (1.9)
75 Part B white capsule	27	1307 (76)	1.5 (0.5-2.3)	4736 (37)	16.8 (6.2)	106 (54.9)	7.8 (2.9)
75 (Study 20) white capsule	28	1365 (68)	1 (0.4-4)	5635 (28)	13.8 (3.7)	125 (65.5)	10.1 (4.5)
100 white capsule	8	1483 (94)	1 (1-2.1)	7055 (42)	15.1 (5.8)	87 (18.9)	6.8 (2.1)
Healthy adult subjects							
Dose (mg)	N	C _{max} (ng/mL) (GCV%) ^a	t _{max} (h) (range) ^b	AUC (ng [*] h/mL) (GCV%) ^a	CL/F (L/h) (GCV%) ^a	V _{ss} /F (L) (GCV%) ^a	t _{1/2} (h) (SD%) ^c
25 (Study 83)	26	409 (37)	1 (0.5-2.5)	1180 (27)	21.1 (27)	160 (29)	8.2 (2.1)
50 (Study 82)	8	944 (37)	1 (1-1.5)	2680 (37)	18.6 (37)	136 (45)	8.0 (1.9)
50 (Study 81)	12	863 (42)	1.5 (1-2.5)	2620 (22)	19.1 (22)	131 (37)	7.3 (2.9)
50 (Study 89)	24	1009 (42)	1 (0.75-2.25)	3004 (25)	17.2 (4.4) ^c	NC	9.7 (2.8)
75 (Study 66) blue capsule	26	1150 (48)	1 (1-4)	3680 (33)	20.4 (33)	131 (39)	7.2 (1.5)
75 (Study 66) white capsule	27	1390 (40)	1 (1-2)	4060 (24)	18.5 (24)	116 (29)	7.5 (1.7)
75 (Study 78)	46	1330 (37)	1 (0.75-4)	3750 (24)	20.0 (24)	156 (31)	10.3 (3.1)
75 (Study 80)	12	1390 (35)	1 (1-4)	4100 (24)	18.3 (24)	170 (31)	14.0 (3.9)
75 (Study 69)	34	1430 (36)	1 (1-3)	4160 (25)	18 (25)	121 (31)	8.3 (1.8)
75 (Study 71)	50	1240 (33)	1 (0.5-2.5)	4070 (25)	18.4 (25)	138 (33)	9.2 (2.6)
75 (Study 85)	22	1440 (37)	1.27 (1-2.5)	4480 (20)	16.7 (20)	128 (27.5)	9.3 (2.6)

Source: GSR summary of clinical pharmacology.

Table 59 N-desmethyl selumetinib PK parameters in healthy subjects and adult patients after single dose

Adult patients with solid tumours (Study 05)							
Dose (mg)	N	C _{max} (ng/mL) (GCV%) ^a	t _{max} (h) (range) ^b	AUC (ng [*] h/mL) (GCV%) ^a	MPR C _{max} (GCV%) ^a	MPR AUC (GCV%) ^a	t _{1/2} (h) (SD) ^c
25 (Study 05)	6	8 (51)	1.7 (1-2)	NC	0.02 (41)	NC	NC
50 (Study 05)	7	17 (72)	1 (1-2)	NC	0.02 (57)	NC	NC
75 (Study 05)	7	78 (68)	1.5 (1-3.95)	820 (72)	0.06 (65)	0.12 (81)	12.7 (NC)
75 (Study 05 Part B)	27	67 (87)	1.5 (0.9-2.3)	405 (32)	0.07 (40)	0.05 (48)	8.8 (NC)
75 (Study 20)	28	76 (52)	1.5 (0.5-4)	446 (35)	0.05 (44)	0.08 (29)	8.6 (4.6)
100 (Study 05)	8	97 (103)	1.5 (1-4)	506 (27)	0.07 (21)	0.08 (14)	8.9 (NC)
Adult healthy adult subjects							
Dose (mg)	N	C _{max} (ng/mL) (GCV%) ^a	t _{max} (h) (range) ^b	AUC (ng [*] h/mL) (GCV%) ^a	MPR C _{max} (GCV%) ^a	MPR AUC (GCV%) ^a	t _{1/2} (h) (SD) ^c
25 (Study 83)	26	36 (38)	1 (0.5-2.5)	98 (25)	0.08 (32)	0.07 (30)	4.7 (2.4)
50 (Study 82)	8	90 (57)	1 (1-2)	276 (42)	0.09 (44)	0.09 (44)	9.2 (3.3)
50 (Study 81)	11	53 (52)	1.5 (1-3)	186 (35)	0.06 (33)	0.07 (38)	5.4 (1.4)
50 (Study 89)	24	73 (55)	1.1 (0.75-2.25)	251 (44)	0.07 (30)	0.08 (35)	10.0 (4.5)
75 (Study 66) white capsule	27	104 (31)	1.5 (1-4)	344 (26)	0.08 (25)	0.08 (24)	7.0 (3)
75 (Study 66) blue capsule	26	90 (56)	1 (1-4)	314 (32)	0.08 (25)	0.08 (20)	6.7 (2.5)
75 (Study 78)	46	95 (35)	1 (0.75-4)	297 (30)	0.07 (22)	0.07 (21) ^d	7.5 (3.4)
75 (Study 80)	12	88 (38)	1.1 (1-4)	315 (25)	0.06 (22)	0.08 (24)	9.6 (4.1)
75 (Study 69)	34	94 (39)	1 (1-3.5)	319 (29)	0.07 (23)	0.08 (23)	7.8 (3.1)
75 (Study 71)	50	90 (38)	1 (0.5-3)	329 (22)	0.07 (21)	0.08 (19)	8.2 (2.8)
75 (Study 85)	22	106 (42)	1.5 (1-3)	404 (27)	0.07 (25.1)	0.09 (25)	9.5 (3.2)

Source: GSR summary of clinical pharmacology.

The PK of selumetinib after multiple dose is studied in both pediatric patients in SPRINT Phase 2 and adult patients in Study 05 as shown in Table 65. The PK parameters after multiple doses were still comparable between adult patients and pediatric patients.

Table 60 Selumetinib PK parameters in pediatric and adult patients after multiple BID doses

Study/ Dose	Number of patients	AUC _{0-12,ss} (ng*h/mL) (CV%) ^a	C _{max,ss} (ng/mL) (CV%) ^a	t _{max,ss} (h) (range) ^b	Rac C _{max} (CV%) ^a	Rac AUC (CV%) ^a
Study 05/ 25 mg	6	1515 (15)	458 (27)	1.28 (1-2)	1.2 (40)	1.3 (37)
Study 05/ 50 mg	7	3381 (43)	987 (34)	1.5 (1-4)	1 (34)	1.3 (0.1)
Study 05/ 75 mg	7	5448 (42)	1439 (29)	1.5 (1-4)	1.2 (65)	1.2 (30)
Study 05/ 100 mg	8	4758 (55)	1365 (41)	1.6 (1-4)	1 (127)	1.5 (28)
SPRINT/ 25mg/m ²	45	1958 (41) ^c	798 (52)	1.5 (0.2-3.2)	1.1 (54)	1.2 (38)

^a Geometric mean, GCV% geometric coefficient of variation

^b Median (range)

^c AUC₀₋₆

AUC_{ss} Area under the plasma concentration time curve at steady state; C_{max,ss} Maximum plasma concentration at steady state; t_{max,ss} Time to reach maximum concentration at steady state; Rac Accumulation ratio.

Data source: Table 11.2.1.2.1, D1532C00005 CSR; Table 11.2.5.2.2, SPRINT Phase II CSR.

Metabolism

The relative contribution to selumetinib turnover by CYP and UGT enzymes was assessed in cryopreserved human hepatocytes in Study BE000021-21, using specific CYP enzyme inhibitors for 3A4 (ketoconazole), 2C19 (ticlopidine), a pan-CYP inhibitor (1-aminobenzotriazole) and a pan-UGT inhibitor (salicylamide). Results indicated that CYP mediated metabolism contributes 56% to the overall metabolism of selumetinib and UGT metabolism contributes 29%.

Study BS0001696-61 was performed to assess the relative contribution of the major CYP isoform involved in the metabolism of selumetinib using recombinant human CYPs (rhCYP) heterologously expressed in baculovirus infected insect cells at 2 and 5 μM selumetinib and 1 μM N-desmethyl selumetinib. Results showed that CYP3A4 accounts for over 85% of selumetinib metabolism in vitro with lesser contributions from CYPs 3A5, 2C19, 2C9, 2E1 and 2D6. The N-desmethyl metabolite formation is predominantly mediated by CYP2C19 with lesser contributions from CYP1A2, 2A6 and 2C9. About 93% of CYP mediated metabolism of N-desmethyl selumetinib is catalyzed by CYP3A4. Moreover, Study KMN012 was also conducted to investigate the metabolism of selumetinib in HLM and heterologously expressed human CYP isoforms. Results indicated that CYP1A2, 2C9 and 2C19 were all capable of N-desmethylation of selumetinib.

Study KMN045 was performed to assess the relative contribution of the major UGT isoform involved in the metabolism of selumetinib by incubations with a range of expressed UGT enzymes in vitro. Results indicated that selumetinib metabolism by hepatic UGT enzymes were extensive and mediated by UGT1A1 and UGT1A3.

Intrinsic Factors

The effect of **ethnicity** on exposure to selumetinib was assessed using pooled data taken from a specific ethnicity study in Asian subjects (Study 86) including Chinese, Japanese, Filipino, Malay, Malaysian, Maldivian, Singaporean, Thai, Vietnamese, Indian and Pakistani, and 9 clinical pharmacology studies in Western subjects (White and Black ethnicities) pooled from Studies 66, 69, 71, 78, 80, 81, 82, 83 and 85. Selumetinib doses were used as 25, 35, 50 and 75 mg single dose in these studies. Table 66 below lists AUC and C_{max} for ethnic comparisons. It is found that after BW or BSA normalization, the differences of mean PK exposure (AUC and C_{max}) between Japanese and Western subjects were reduced from approximately 1.6-1.8-fold higher to approximately 1.4- to 1.7-fold higher. Further comparison of selumetinib PK in Japanese, Chinese, and Western subjects (not shown here) revealed that BW or BSA based dose has brought a general overlap of distribution of individual AUC or C_{max} among Chinese, Japanese, and Western subjects.

Table 61 PK ethnic comparison of selumetinib after single dose

PK parameters Geomean (CV%)	Japanese ^a (N=27)	Chinese ^b (N=7)	Western ^c (N=52)	Geometric mean ratio	
				J/W (90% CI)	C/W (90% CI)
AUC/Dose (h*ng/mL/mg)	85 (21)	73 (11)	51 (29)	1.65 (1.52, 1.79)	1.40 (1.22, 1.61)
AUC _{weight,norm} ^d (h*ng/mL/mg*kg)	5680 (22)	4830 (16)	3950 (28)	1.42 (1.30, 1.54)	1.19 (1.03, 1.38)
AUC _{BSA,norm} ^e (h*ng/mL/mg*m ²)	153 (20)	131 (13)	99 (28)	1.52 (1.41, 1.64)	1.29 (1.13, 1.47)
C _{max} /Dose (ng/mL/mg)	28.7 (36)	21.7 (39)	15.5 (43)	1.81 (1.60, 2.06)	1.38 (1.11, 1.73)
C _{max,weight,norm} (ng/mL/mg*kg)	1920 (38)	1430 (40)	1210 (44)	1.56 (1.38, 1.77)	1.17 (0.92, 1.48)
C _{max,BSA,norm} (ng/mL/mg*m ²)	51.6 (36)	38.7 (39)	30.2 (43)	1.67 (1.48, 1.89)	1.26 (1.01, 1.59)

^a Japanese HVs from Study 86

^b Chinese (by ethnicity) HVs from Study 86

^c Western HVs from Study 66

^d Body weight normalised AUC: AUC_{weight,norm} = AUC/Dose*BW

^e BSA normalised AUC: AUC_{BSA,norm} = AUC/Dose*BSA

J/W Japanese to Western ratio; C/W Chinese to Western ratio.

Source: Table 11.2.2.1, D1532C00066 CSR; Table 11.2.2.1, D1532C00086 CSR.

The **Renal Impairment** study was conducted with a single oral 50 mg selumetinib dose (capsule) in adult subjects with normal renal function and in subjects with end stage renal disease (ESRD) in Study 81. Table 67 shows selumetinib PK exposure in the study. Results showed that both

selumetinib exposure and plasma protein binding were lower in the ESRD group, leading to a similar unbound selumetinib exposure. In the ESRD group, selumetinib was administered to subjects with ESRD both before and after a dialysis session to investigate whether dialysis would make a change of selumetinib PK. Results showed that total selumetinib exposure was slightly lower (~ 17% for AUC and 30% for C_{max}) when dosed before dialysis than after dialysis, however exposure was highly variable and a decrease of >15% was only observed in 7 out of 12 subjects. Similar results were found for the N-desmethyl metabolite. The data suggest that dialysis have minimal effect on the removal of systemic selumetinib and N-desmethyl selumetinib.

Table 62 Selumetinib PK parameters in adult subjects with normal and ESRD subjects prior and post dialysis treatments

Parameter (units)	Normal (N=11)	Period 1 (N=12)	Period 2 (N=12)
AUC (ng·h/mL) (GCV%) ^a	2620 (22)	1880 (36)	1560 (44)
AUC _u (ng·h/mL)(GCV%) ^a	10.6 (23)	10.3 (20)	NA
C _{max} (ng/mL)(GCV%) ^a	863 (42)	725 (46)	507 (50)
C _{max,u} (ng/mL)(GCV%) ^a	3.48 (43)	3.95 (35)	NA
t _{max} (h)(Range) ^b	1.5 (1-2.5)	1 (0.5-2.5)	1.5 (0.50-2)
t _{1/2} (h)(SD) ^c	7.3 (2.9)	6.6 (1.78)	5.8 (2.1)
CL/F (L/h)(GCV%) ^a	19.1 (22)	26.6 (36)	32.2 (44)
CL/F _u (L/h)(GCV%) ^a	4740 (23)	4880 (20)	NA

^a Geometric mean (GCV%) geometric coefficient of variation

^b Median (range)

^c Arithmetic mean (SD)

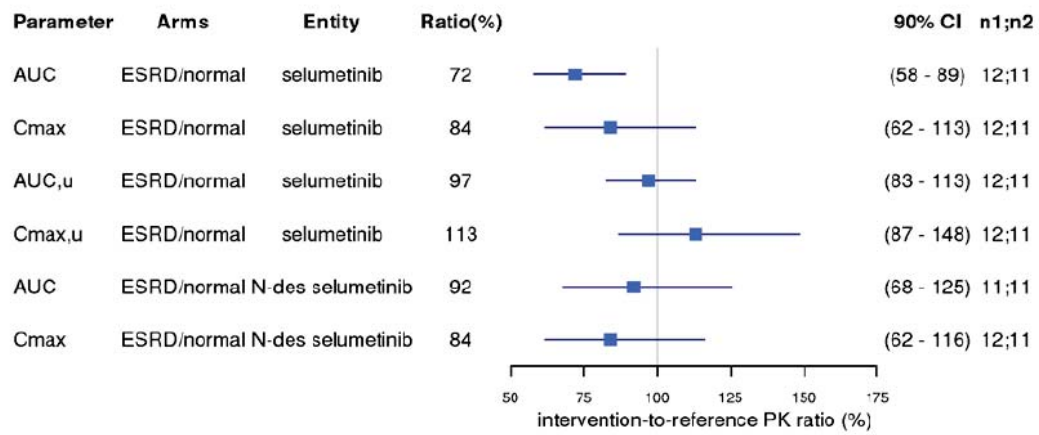
Treatment Period 1: single 50 mg administration on day 1 after completion of a dialysis session.

Treatment Period 2: single 50 mg dose of selumetinib, 1 hour prior to the start of a dialysis session.

AUC Area under the plasma concentration time curve; AUC_u Area under the unbound plasma concentration time curve; C_{max} Maximum plasma concentration; C_{max,u} Maximum unbound plasma concentration; CL/F Apparent clearance; CL/F_u Unbound apparent clearance GCV% Geometric coefficient of variation; N Number of subjects enrolled to the study; NA Not applicable; t_{1/2} Half-life; t_{max} Time to reach maximum concentration; V_{ss}/F Apparent volume of distribution.

Source: Table 11.2.4 (from Section 11.2) D1532C00081 CSR.

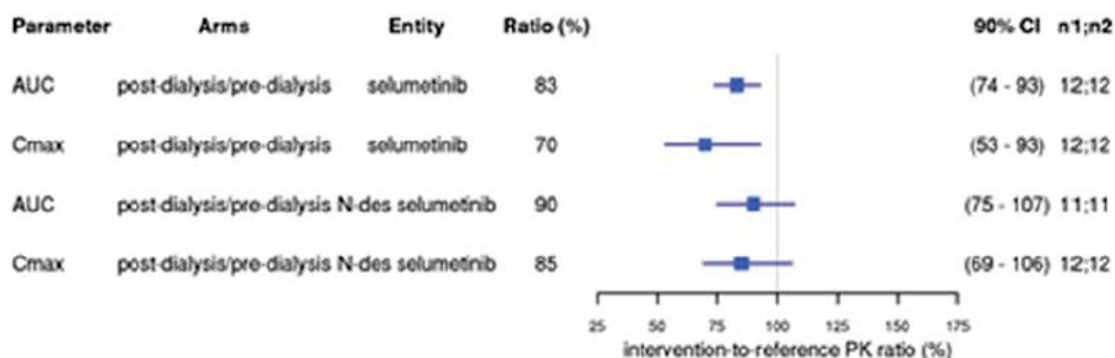
Figure 15 Normal vs. ESRD subjects - GLS mean ratios and 90% CIs for AUC and Cmax for total and unbound selumetinib and N-desmethyl selumetinib (Study 81)



Normal: CrCL >80 mL/min; single 50 mg administration of selumetinib on Day 1; ESRD: CrCL <30 mL/min, requiring haemodialysis, no CrCL calculation. For ESRD subjects, only data from off dialysis (Period 1) was included in these analyses.

Source: GSR summary of clinical pharmacology.

Figure 16 Pre- vs. post-dialysis ESRD subjects - GLS mean ratios and 90% CIs for AUC and Cmax for total and unbound selumetinib and N-desmethyl selumetinib (Study 81)



ESRD: CrCL <30 mL/min, requiring haemodialysis

Treatment Period 1: single 50 mg administration on day 1 after completion of a dialysis session.

Treatment Period 2: single 50 mg dose of selumetinib, 1 hour prior to the start of a dialysis session.

Results based on linear fixed effect analysis of variance model using the logarithm of AUC and C_{max} as the response variable and period as a fixed effect.

Source: GSR summary of clinical pharmacology

The **Hepatic Impairment** study 82 was conducted with a single 50 mg oral selumetinib capsule dose in adult subjects with normal and mild hepatic impairment, a 50 or 25 mg dose in subjects with moderate hepatic impairment, and a 20 mg dose in subjects with severe hepatic impairment. Classification of hepatic impairment was performed using the Child-Pugh classification system. The PK results are listed in Table 68 and statistical evaluation is in

Table 69.

Table 63 Selumetinib and N-desmethyl selumetinib PK parameters in adult subjects with normal, mild, moderate, and severe hepatic impairment (Study 82)

Parameter (units)	Selumetinib				N-desmethyl selumetinib			
	Normal N=8	Mild N=8	Moderate N=8	Severe N=8	Normal N=8	Mild N=8	Moderate N=8	Severe N=8
AUC _D (ng*hr/mL/mg) ^a	53.6 (37)	45.9 (39)	85.1 (38)	84.3 (20)	5.5 (42)	3.2 (45)	3.5 (68)	NA
AUC _u _D (ng*hr/mL/mg) ^a	0.184 (30)	0.127 (41)	0.259 (53)	0.583 (45)	0.045 (11)	ND	NA	NA
C _{max} _D (ng/mL/mg) ^a	18.9 (37)	14.8 (47)	23.6 (37)	18.5 (50)	1.81 (57)	0.80 (58)	0.55 (103)	0.17 (44)
C _{max, u} _D (ng/mL/mg) ^a	0.065 (32)	0.040 (55)	0.072 (51)	0.128 (73)	0.018 (29)	ND	NA	NA
t _{max} (h) ^b	1 (1-1.5)	1.25 (0.5-4)	1 (1-1)	1 (0.5-2)	1 (1-2)	1.5 (1-4)	1.25 (1-1.5)	2 (1.5-2)
t _{1/2} (h) ^c	8.0 (1.9)	7.7 (2.3)	9.9 (2.6)	9.0 (1.3)	9.2 (3.3)	5.2 (1.5)	7.7 (2.9)	NA
CL/F (L/h) ^a	18.6 (37)	21.8 (39)	11.7 (46)	11.9 (20)	NA	NA	NA	NA
MPR AUC _(0-t) ^a	NA	NA	NA	NA	0.09 (44)	0.05 (59)	0.02 (159)	ND
MPR C _{max} ^a	NA	NA	NA	NA	0.09 (44)	0.05 (62)	0.02 (140)	0.007 (29)

^a Geometric mean (GCV%)

^b Median (range)

^c Arithmetic mean (SD)

Dose normalised parameters summarise subjects dosed with both the 25 mg and 50 mg dose; other parameters summarise those of the 50 mg dose only.

Mild: (Child-Pugh A) single oral dose of 50 mg selumetinib; Moderate: (Child-Pugh B) 6 subjects received single oral dose of 50 mg and 2 subjects (b) (6) received 25 mg selumetinib; Severe: (Child-Pugh C) single oral dose of 20 mg selumetinib; Normal: single oral dose of 50 mg selumetinib.

AUC_D Area under the plasma concentration-time curve from time zero to infinity divided by dose;

C_{max}_D Maximum observed concentration in plasma divided by dose; AUC_u_D Unbound area under the plasma concentration-time curve from time zero to infinity divided by dose; C_{max, u}_D Unbound maximum observed concentration in plasma divided by dose; GCV% Geometric coefficient of variation; MPR Metabolite to parent ratio; n Number of subjects; NA Not applicable; ND Not determined; t_{max} Time to C_{max}; t_{1/2} Terminal half-life.

Source: Table 11.2.3.1, Table 11.2.3.2, Table 11.2.4.1 and Table 11.2.4.2 (from Section 11.2) Study 82 CSR.

Table 64 Statistical evaluation of selumetinib PK in hepatic impairment study (82)

Selumetinib	Parameters	Mild/normal	Moderate/normal	Severe/normal
Total exposure	AUC/dose (90% CI)	0.86 (0.64, 1.14)	1.59 (1.19, 2.11)	1.57 (1.18, 2.09)
	C _{max} /dose (90% CI)	0.78 (0.55, 1.11)	1.25 (0.88, 1.77)	0.98 (0.69, 1.39)
Unbound exposure	AUC _u /dose (90% CI)	0.69 (0.49, 0.98)	1.41 (0.99, 2.00)	3.17 (2.24, 4.50)
	C _{max,u} /dose (90% CI)	0.63 (0.41, 0.97)	1.11 (0.72, 1.70)	1.98 (1.29, 3.04)

Source: GSR Study 82 CSR.

Extrinsic Factors

Food Effect

The effect of a high fat meal on the exposure of blue selumetinib capsules was investigated in healthy adult subjects (Study 69), and in adult patients (Study 20). In addition, the effect of low-fat meal on the blue capsule was investigated in Study 89. Selumetinib PK parameters in the fasted and the fed states across all studies presented in Table 70.

Table 70 Selumetinib PK parameters in the fasted and fed states across all food effect studies

Parameter (unit)	Study 69 (high fat meal) N=34 75 mg blue capsule		Study 20 (high fat meal) N=28 75 mg blue capsule		Study 89 (low fat meal) N=24 50 mg blue capsule	
	Fed	Fasted	Fed	Fasted	Fed	Fasted
AUC (ng·h/mL) (GCV%) ^a	3490 (25)	4160 (25)	4586 (35)	5635 (28)	1871 (39)	3004 (25)
C _{max} (ng/mL) (GCV%) ^a	711 (33)	1430 (36)	514 (54)	1365 (68)	404 (52)	1009 (42)
t _{max} (h) (Range) ^b	2.5 (1-6)	1 (1-3)	4 (1-11.6)	1 (0.4-4)	2 (0.1-3.5)	1.14 (0.75-2.25)
t _{1/2} (h) (SD) ^c	8.0 (2.4)	8.3 (1.8)	9.1 (3.8)	10.0 (4.5)	11.9 (2.7)	9.7 (2.8)
CL/F (L/h) (GCV%) ^a	21.5 (25)	18 (25)	16.3 (35)	13.3 (28)	28.5 (10.2) ^c	17.2 (4.4) ^c

^a Geometric mean (GCV%)

^b Median (range)

^c Arithmetic mean (SD)

AUC Area under the plasma concentration-time curve; C_{max} Maximum observed concentration in plasma; CL/F Apparent oral plasma clearance; GCV% geometric coefficient of variation; N Number of subjects; t_{max} Time to C_{max}; t_{1/2} Apparent terminal half-life.

Source: Table 11.2.3, Clinical Study Report D1532C00069; Table 14.2.2.1, D1532C00089 CSR; Table 11.2.1.9 D1532C00020 CSR.

The N-desmethyl metabolite had limited detectable concentrations in the low fat meal study, given conversion from parent compound was low with geometric mean metabolite to parent ratios at ~7% for AUC and C_{max} and lower doses of selumetinib was administered resulted in limited detectable concentrations of the metabolite. The observed difference between fed and fasted treatments in the high fat meal studies were similar to those observed for the parent compound.

Drug-Drug Interaction

In Vivo Studies

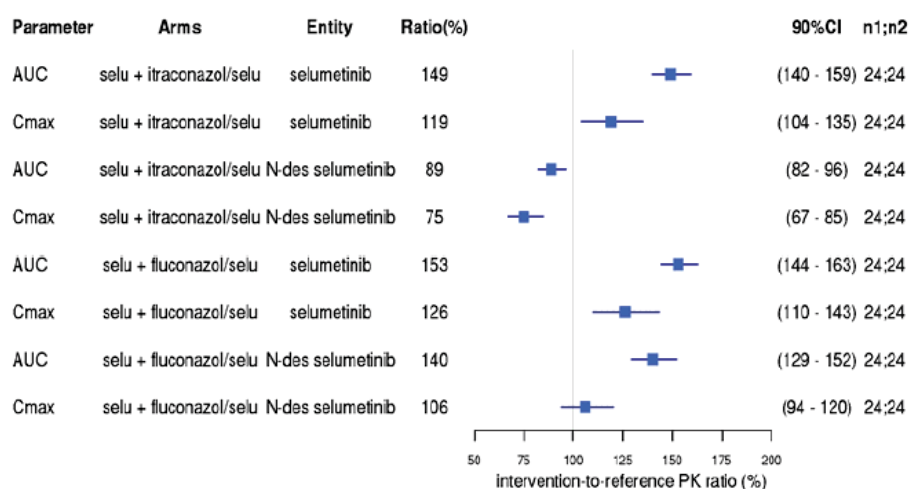
The extent and significance of any inhibition on the metabolism of selumetinib by Itraconazole (strong CYP3A4 inhibitor) and by fluconazole (strong CYP2C19/moderate CYP3A4 inhibitor) was assessed following administration of single 25 mg dose of selumetinib in healthy adult subjects. Itraconazole (200 mg BID) or fluconazole (200 mg QD) were administered in separate periods for 8 days to maximize the degree of CYP inhibition in Study 83. Selumetinib was dosed prior to the CYP inhibitors and after 8 days. The PK and statistical comparisons for selumetinib and N-desmethyl metabolite are shown in Table 71 and Figure 17.

Table 71 Selumetinib and N-desmethyl selumetinib PK parameters with and without itraconazole and fluconazole in Study 83

Parameter (units)	Selumetinib			N-desmethyl selumetinib		
	Alone N=26	+itraconazole N=24	+fluconazole N=22	Alone N=26	+itraconazole N=24	+fluconazole N=22
AUC ^a (ng·h/mL)	1180 (27)	1760 (32)	1770 (33)	83 ^a (30)	75 ^a (29)	117 ^a (30)
C _{max} ^a (ng/mL)	409 (37)	484 (31)	509 (34)	36 (38)	27 (29)	38 (34)
t _{max} (h) ^b	1 (0.5-2.5)	1 (0.5-2.5)	1.5 (0.5-2.5)	1 (0.5-2.5)	1.5 (1-2.5)	1.5 (1-2.5)
t _{1/2} (h) ^c	8.2 (2.1)	14.0 (7.8)	9.8 (3.1)	4.7 (2.4)	4.5 (1.8)	6.4 (3.7)
CL/F (L/h) ^a	21.1 (27)	14.2 (32)	14.1 (33)	NC	NC	NC
MPR AUC _(0-t) ^a	NA	NA	NA	0.07 (30)	0.04 (33)	0.07 (35)
MPR C _{max} ^a	NA	NA	NA	0.09 (32)	0.05 (29)	0.07 (31)

Source: Table 11.2.4 and Table 11.2.5 (from Section 11.2) D1532C00083 CSR.

Figure 17 Effect of itraconazole and fluconazole on the exposure of selumetinib and N-desmethyl selumetinib by linear mixed-effect analysis



Source: GSR summary of clinical pharmacology.

The effect of multiple doses of rifampicin (strong inducer of CYP3A4/5, 2C19, and UGT1A1) was assessed following administration of single 75 mg dose of selumetinib in healthy adult subjects.

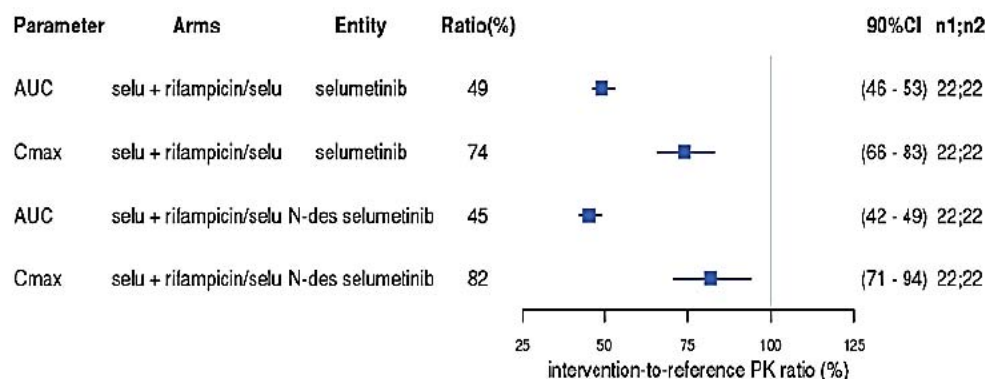
Rifampicin 600 mg QD were administered for 8 days to maximize the degree of CYP induction in Study 85. Adequate level of rifampicin was demonstrated by a 3.4-fold increase in the 4β-hydroxycholesterol/cholesterol ratio, and this was maintained to the end of the PK assessment. The PK and statistical comparisons for selumetinib and N-desmethyl metabolite are shown in Table 72 and Figure 18.

Table 72 Selumetinib and N-desmethyl selumetinib PK parameters with and without rifampicin in Study 85

Parameter (units)	Selumetinib		N-desmethyl selumetinib	
	Selumetinib alone N=22	Selumetinib +rifampicin N=22	Selumetinib alone N=19	Selumetinib +rifampicin N=22
AUC (ng·h/mL) ^a	4480 (20)	2200 (23)	404 (27)	170 (28)
C _{max} (ng/mL) ^a	1440 (36.5)	1070 (38)	106 (42)	87 (40)
t _{max} (h) ^b	1.27 (1-2.5)	1 (0.5-2)	1.5 (1-3)	1 (1-2.5)
t _{1/2} (h) ^c	9.3 (2.6)	6.7 (2.3)	9.5 (3.2)	2.7 (0.7)
CL/F (L/h) ^a	16.7 (20)	34.1 (23)	NC	NC
MPR AUC ^a	NA	NA	0.09 (25)	0.07 (19)
MPR C _{max} ^a	NA	NA	0.07 (25)	0.08 (20)

Source: Table 11.2.4 and Table 11.2.5 (from Section 11.2) Clinical Study Report D1532C00085.

Figure 18 Effect of rifampicin on the exposure of selumetinib and N-desmethyl selumetinib by linear mixed-effect analysis



Source: GSR summary of clinical pharmacology.

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Additionally, the Applicant calculated exposure matrices with consideration of exposure and potency of each active moiety, i.e., total and unbound selumetinib and N-desmethyl metabolite respectively as listed in Table 69, based on the following equations:

$$\text{Total moiety AUC} = AUC_{parent}/MW_{parent} + AUC_{met}/MW_{met}$$

$$\text{Adjusted total moiety AUC} = AUC_{parent}/MW_{parent} \times \frac{1}{IC50_{parent}} + AUC_{met}/MW_{met} \times \frac{1}{IC50_{met}}$$

$$\text{Adjusted unbound moiety AUC} = AUC_{parent}/MW_{parent} \times \frac{fu_{parent}}{IC50_{u,parent}} + AUC_{met}/MW_{met} \times \frac{fu_{met}}{IC50_{u,met}}$$

MW_{parent} = 457.7 g/mol; MW_{met} = 443.7 g/mol;

In vitro unbound fraction: 0.016 (parent) and 0.021 (metabolite);

IC₅₀ (parent) = 5.308 nM; IC₅₀(metabolite) = 1.561 nM, based on average of 6 cell lines in GSR 2.2.2.6.2.

Table 73 Selumetinib and N-desmethyl selumetinib calculated molar parameters in drug interaction studies

Component	Study and dose	Selumetinib (geomean (CV%))		N-desmethyl Selumetinib (geomean (CV%))		Total Moiety		Adjusted total moiety		Adjusted unbound moiety	
		AUC (ng ^h /mL)	Cmax (ng/mL)	AUC (ng ^h /mL)	Cmax (ng/mL)	AUC (nM ^h)	Cmax (nM)	AUC	Cmax	AUC	Cmax
Selumetinib	83/ 25 mg	1180	409	83.4	35.7	2766	974	606	219.9	401	14.6
Sel + itra	83/ 25 mg	1760	484	74.6	27	4013	1118	832	238.2	54.8	15.7
Sel + fluc	83 / 25 mg	1770	509	117	37.5	4131	1197	897.5	263.7	59.4	17.5
Selumetinib	85 / 75 mg	4480	1440	404	106	10699	3385	2427	745.8	161.3	49.4
Sel +rif	85/ 75 mg	2200	1070	170	86.9	5190	2534	1151	565.9	76.3	37.5

Source: GSR 1.11.3 Table 1.

A new statistical comparison on AUC is shown in Table 74.

Table 65 Summary of statistical results for DDI studies

	Dose regimen	Selumetinib AUC (ng.hr/mL)		N-desmethyl-Selumetinib AUC (ng.hr/mL)		Selumetinib AUC ratio	Total moiety AUC ratio	Adjusted total moiety AUC ratio	Adjusted free total moiety AUC ratio
		Drug	Drug +inh	Drug	Drug +inh				
DDI									
ITZ	25 mg alone or +200 mg BID ITZ for 8 days	1180	1760	83.4	74.6	1.49	1.45	1.37	1.36
FLC	25 mg alone or + 400 mg D1 and 200 mg for 7 days	1180	1770	83.4	117	1.50	1.49	1.48	1.48
RIF	75 mg alone or with 600 mg rifampicin for 8 days	4480	2200	404	170	0.49	0.485	0.474	0.470

Source: GSR 1.11.3 Table 3.

In Vitro Studies

The potential inhibitory effect of selumetinib (0.05 to 50 μ M) on the major human hepatic cytochrome P450 enzyme activities was evaluated in pooled human liver microsomes. Selumetinib showed little or no inhibitory effect against any of these CYP enzymes to a clinically relevant extent.

Table 66 Mean IC₅₀ values (mM) for the inhibition of CYPs by selumetinib in pooled HLM

Parameter	1A2	2A6	2C8	2C9	2C19	2B6	2D6	2E1	3A4 ^a	3A4 ^b
IC ₅₀ selumetinib	>70	NI	>70	52.1	>70	53.1	45.3	NI	>70	>70
Ki ^c	NA	NA	NA	26.1	NA	26.6	22.7	NA	NA	NA
% inhibition ^d	24.6	NA	27.2	NA	25.2	NA	NA	NA	41.3	34.9
R ₁	NA	NA	NA	1.00	NA	1.00	1.00	NA	NA	NA
R _{1gut}	NA	NA	NA	NA	NA	NA	NA	NA	13.5	13.5
R _{imax}	NA	NA	NA	0.001	NA	0.001	0.001	NA	NA	NA

^a CYP3A4 nifedipine substrate site

^b CYP3A4 midazolam substrate site

^c Estimated Ki=IC₅₀/2 as probe substrates at about Km

^d % inhibition at the maximum assay concentration where no IC₅₀ obtained

$R_1 = 1 + [I_{maxu}] / K_i$, where I_{maxu} is the unbound plasma C_{max} , FDA criteria ≥ 1.02 indicates DDI risk cannot be excluded.

$R_{1gut} = 1 + [I_{gut}] / K_i$, where I_{gut} is the estimated maximal gut lumen concentration, FDA criteria ≥ 11 indicates DDI risk cannot be excluded.

$R_{imax} = [I_{maxu}] / K_i$ where I_{maxu} is the unbound plasma C_{max} , EMA criteria ≥ 0.02 indicates DDI risk cannot be excluded.

C_{max} Maximum plasma concentration; DDI Drug-drug interaction; EMA European Medicines Agency; FDA Food and Drug Administration; IC₅₀ Half maximal inhibitory concentration; Ki Inhibition constant; NA Not assessed, no inhibition observed over the concentration range of the assay (up to 70µM); NI No inhibition observed over the concentration range of the assay (up to 70µM).

Source: Section 2.6.4.7.2.5 of the Non-clinical Summary.

The potential induction of selumetinib on CYP450 enzymes were assessed in human hepatocytes. Selumetinib induction of CYP1A and CYP3A were only observed at the higher concentrations tested (10 and 30 µM, 5 to 15-fold higher than C_{max} after 75 mg dose). No significant induction of activity was observed for CYP2C9 in donor I (<10% of rifampicin response in donor I). Selumetinib showed no induction of CYP1A2 mRNA or CYP2B6 mRNA expression or enzyme activity at concentrations up to 100 µM.

Following co-incubation of UGT1A1 and UGT2B7 in HLM with selumetinib at concentrations up to 100 µM, weak inhibition of enzyme activity was observed with IC₅₀ >100 µM.

The effect of selumetinib on the inhibition of the hepatic transporters OCT1, OATP1B1 and OATP1B3 was investigated in vitro (making the assumption that IC₅₀=Ki).

Table 67 Inhibition of hepatic uptake transports by selumetinib

Transport protein	Test system	Probe substrate	IC ₅₀ (µM) ^a	IC ₅₀ /25 x [I _{in free}] ^b	R-value ^c
OATP1B1	HEK-293	[² H]-estradiol glucuronide	8.76	2.47	1.02
OATP1B3	HEK-293	[² H]-estradiol glucuronide	19.0	5.35	1.01
OCT1	HEK-293	[¹⁴ C]-TEA	none	NC	NC

^a IC₅₀ assumed to equal K_i

^b EMA 2012: Clinically relevant inhibition of hepatic drug transporter unlikely when K_i ≥ 25 x [I_{in free}]

^c FDA 2017: Clinically relevant inhibition of hepatic drug transporter unlikely when R ≤ 1.1.

$$R = 1 + (I_{in\ max} \times fu / IC_{50})$$

EMA European Medicines Agency; FDA Food and Drug Administration; IC₅₀ Half maximal inhibitory concentration; K_i Inhibition constant; NC Not calculated.

Source: Section 2.6.4.7.6.3 of the Non-clinical Summary.

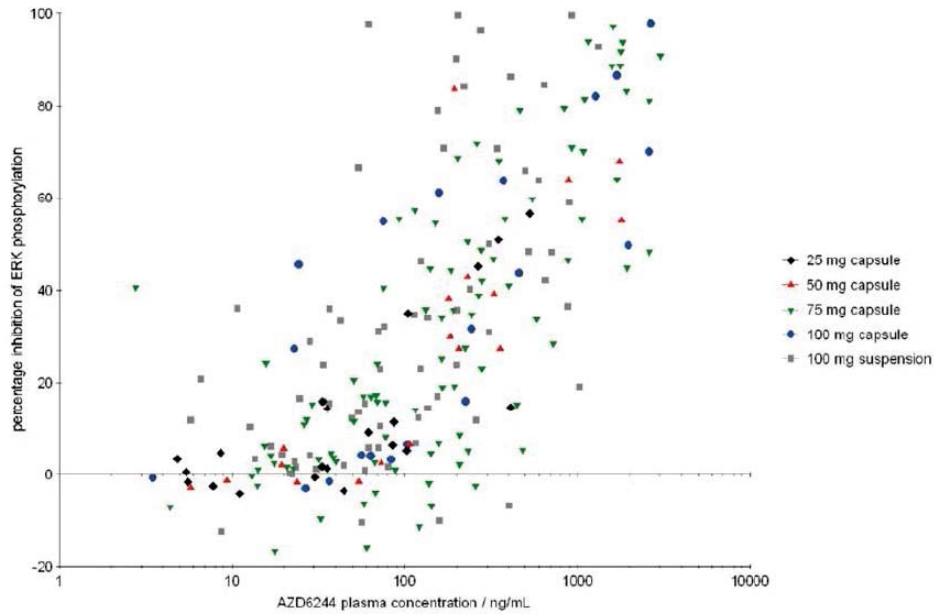
An in vitro study using the MDCKII-MDR1 cell system indicated that selumetinib (tested at 1, 10, 25 and 50 µM) is a substrate of MDR1 (P-gp). The MDCKII-corrected efflux ratio (ER) was between 6.1 to 12.7.

The potential inhibitory effect of N-desmethyl selumetinib was assessed with individual human CYP isoforms in vitro using selective marker substrates. N-desmethyl selumetinib showed minor inhibition of CYP2C8, 2C9, 2C19, 2D6 and 2E1, and was found to be a direct inhibitor of CYP1A2 and CYP3A4 (testosterone), with IC₅₀ values of 18.9 µM and 26.3 µM for CYP1A2 and CYP3A4 (testosterone) respectively. The results suggested a minimal inhibition effect on CYP1A2 and 3A4 substrates at steady state by using the estimated free plasma concentration (28.5 ng/mL) from available clinical data (total C_{max} 1.5 µg/mL).

Clinical Pharmacodynamics

Given selumetinib is a MEK1/2 inhibitor and ERK is the substrate of MEK, measuring the inhibition of phosphorylation of ERK following selumetinib administration is considered an indirect measure of MEK inhibition by selumetinib, as assessed in Study 05 at 4 time points post single dose administration in both Part A (Day 1) and Part B (Days 1 and 8) in all patients in adult patients with advanced malignancies. There is a direct relationship between selumetinib plasma concentration and the inhibition of pERK, with the highest inhibition occurring at the higher selumetinib plasma concentrations.

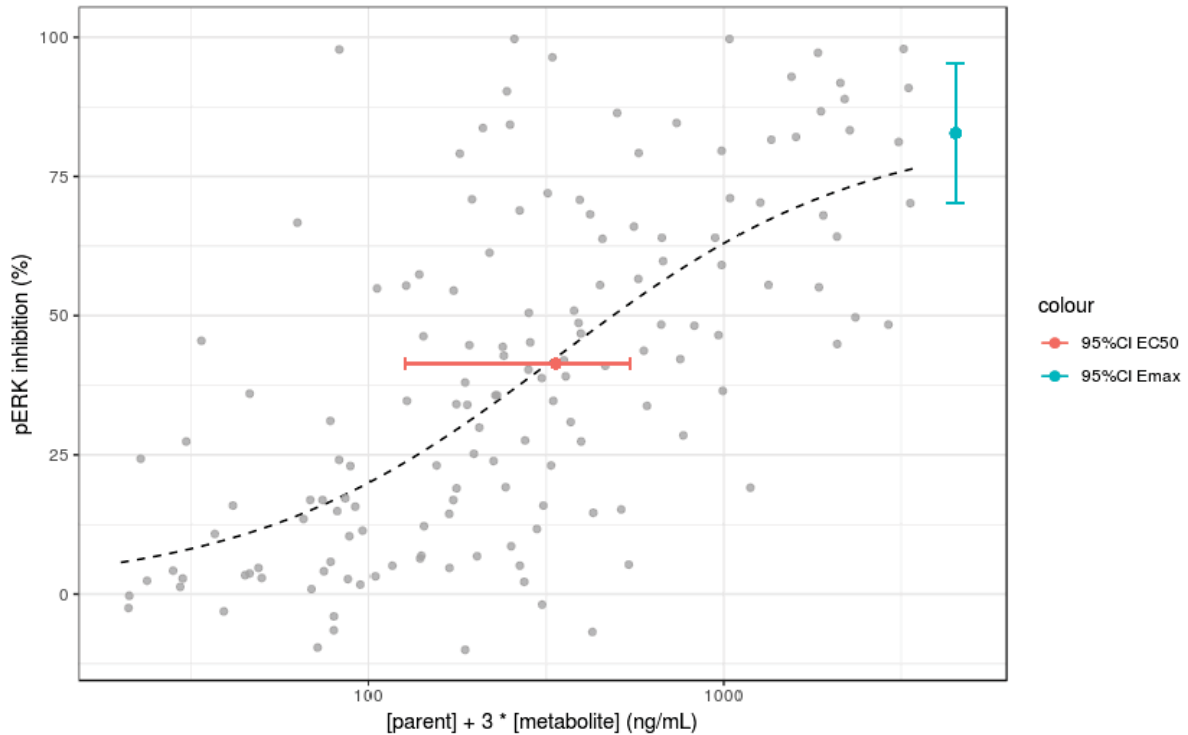
Figure 19 pERK inhibition versus selumetinib plasma concentration in Study 05 in adult patients



Source: Figure 13, Clinical Study Report D1532C00005.

The potential contribution from the active N-desmethyl metabolite, which is ~7% of parent drug plasma concentration but 3-5 fold potent than selumetinib was further considered. Therefore, plasma concentration data for selumetinib and N-desmethyl selumetinib were combined to provide a plasma concentration for the active moiety, with the metabolite concentrations increased with a weighting to account for an increase in in vitro potency of 3-fold compared to parent. An E_{max} model was used to describe the relationship between active moiety concentrations and pERK inhibition.

Figure 20 Relationship between pERK inhibition and plasma concentration of selumetinib active moiety



Source: GSR summary of clinical pharmacology.

19.4.3. Population PK and Exposure-Response Analysis

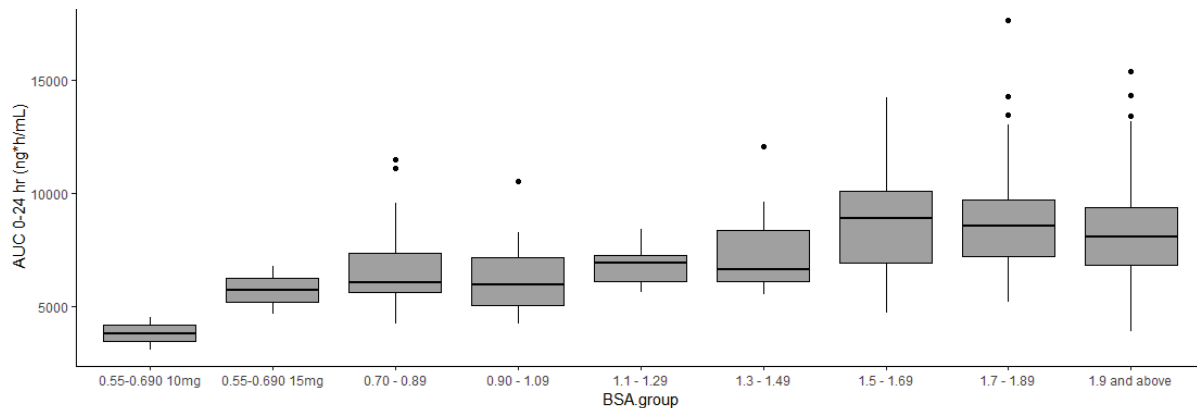
Key Review Questions

1. Is the proposed dosing regimen acceptable for patients with lowest BSA (0.55-0.69 m²)?

No. New dose recommendation of morning dose 20 mg and evening dose 10 mg for this subgroup of patients. Sponsor proposed (b) (4)

We recommend morning dose of 20 mg and evening dose 10 mg for this subgroup and it could bring AUC comparable with other groups (Figure 21). Notably, the two individuals in clinical trial has 0.67 m² BSA received 20mg BID dosing regimen instead of (b) (4)

Figure 21 Plot of Patients AUC Across BSA Bands



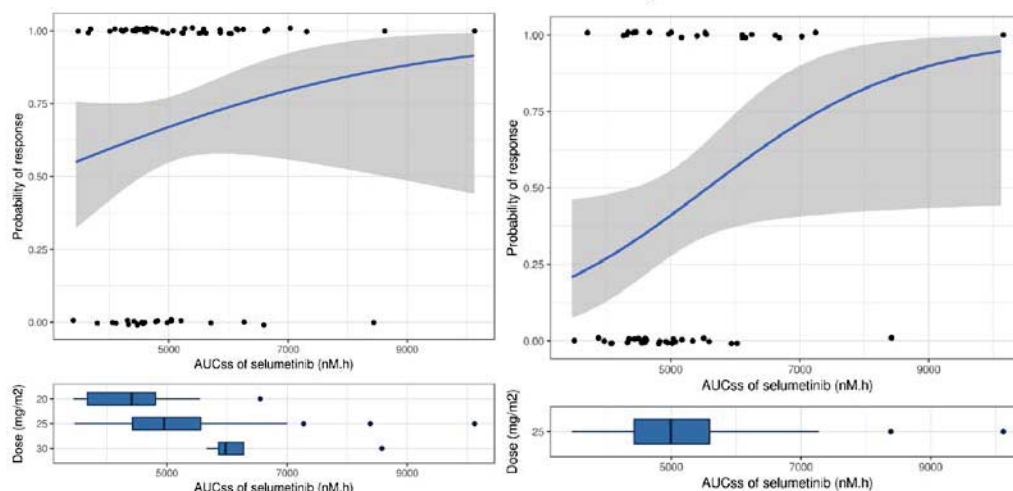
Source: Reviewer's independent analysis.

2. Exposure-response analysis relationship for efficacy.

The final E-R analysis dataset for ORR included 68 subjects in the NCI central analysis dataset and 50 subjects in the independent central review dataset. NCI central analysis dataset included patient data from both Phase I and Phase II Stratum 1 studies, and independent central review only analyzed efficacy data from patients in the Phase II study.

Binomial logistic regression was further performed on AUCs of selumetinib versus response to assess if there is any significant E-R relationship in the NCI central analysis dataset (Figure 22 Left), as well as independent central review dataset (Figure 22 Right). The logistic regression suggested there was no significant exposure-ORR relationship in the NCI central analysis dataset (p-value of coefficient: 0.203), while a barely significant exposure-ORR relationship was found in the independent central review dataset (p-value of 0.0428).

Figure 22 Binomial logistic regression on AUCss of selumetinib (Left: NCI central analysis. Right: Independent central review)



Source: figure 13 of Pop-PK report.

Reviewer's comment: The Applicant's ER analysis is acceptable. Exposure-response assessment demonstrated a positive trend for AUCss-efficacy (ORR) association. The exposure-response assessment should be interpreted with caution because of the limitation of the study design (e.g., a single dose level pivotal trial with a small number of subjects and a high dose interruption rate).

3. What is the exposure response relationship for safety?

No clear E-R relationship between selumetinib and/or N-desmethyl metabolite exposure and 13 relevant AEs (rash acneiform, rash non-acneiform, nail disorders, oral mucositis, leukopenic events, thrombocytopenic events, erythropenic events, LVEF reduction, CK elevation, nausea, vomiting, diarrhoea and hepatic events).

No clear E-R relationship between exposure and AEs leading to discontinuation, dose interruption or reduction.

Reviewer's comment: The Applicant's ER analysis for safety is acceptable.

4. Population PK model

The PK of selumetinib was well-described by a two-compartment model with first-order elimination and sequential zero- and first-order delayed absorption. A one-compartment model reasonably described the N-desmethyl metabolite plasma concentrations over time.

For all covariates evaluated, BSA had an impact on CL, V2, Fm/V4 and V3. AGE and RACE were also found to have a minor impact on selumetinib PK, while only BSA had a >20% impact on CL, which is considered clinically relevant. None of other covariates including formulation, gender,

CrCL, bilirubin, albumin, ALT, has any significant impact on selumetinib and/or N-desmethyl metabolite PK.

There was no relevant difference in PK between patients and healthy subjects.

Figure 23: Parameter estimates for the final PopPK selumetinib and N-desmethyl selumetinib PopPK base model

Parameter	Description	Final model			Bootstrap		
		Estimate	RSE ^a (%)	Shrinkage (%)	Median	2.50%	97.50%
θ1	Plasma clearance parent, CL (L/h)	11.6	4.0	-	11.6	11.0	12.2
θ2	Selumetinib central volume of distribution, V2 (L)	29.6	4.4	-	29.6	27.5	31.6
θ3	Selumetinib inter-compartmental clearance, Q (L/h)	7.97	4.2	-	8.00	7.40	8.63
θ4	Selumetinib peripheral volume of distribution, V3 (L)	49.7	4.2	-	49.6	46.8	52.9
θ5	Selumetinib absorption rate constant, Ka (h ⁻¹)	4.87	8.6	-	4.80	4.23	5.49
θ6	Duration of zero-order selumetinib absorption, D ₁ (h)	0.53	2.4	-	0.54	0.51	0.57
θ7	Selumetinib bioavailability, F ₁ (fraction)	0.66	3.9	-	0.66	0.63	0.69
θ8	Selumetinib absorption lag time (h)	0.25	0.0	-	0.25	0.24	0.26
θ9	Fraction metabolised to N-desmethyl selumetinib, F _m (fraction)	0.075	6.9	-	0.08	0.06	0.09
θ10	N-desmethyl selumetinib plasma clearance, CL _m (L/h)	10.6	5.6	-	10.7	8.71	12.5
θ11	Age on CL CL=TV*(Age/29) ^θ	-0.12	20.0	-	-0.13	-0.19	-0.07
θ12	BSA on CL CL=TV*(BSA/1.8) ^θ	0.97	6.4	-	0.98	0.82	1.13
θ13	RACE on CL (reference non-Asian - 100%) Asian race	-19%	11.2	-	-0.19	-0.23	-0.15
θ14	BSA on F _m F _m =TV*(BSA/1.8) ^θ	-1.00	7.3	-	-0.99	-1.11	-0.87
θ15	BSA on V2 V2=TV*(BSA/1.8) ^θ	1.57	4.4	-	1.62	1.25	1.90
θ16	BSA on V3 V3=TV*(BSA/1.8) ^θ	0.97	11.7	-	1.08	0.58	1.41

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Inter-individual variability							
ω_1	IIV in CL (CV%)	23	4.2	9.7	23	21	25
$\omega_{1,2}$	Correlation CL~V2 (%)	63	7.0	-	61	58	63
ω_2	IIV in V2 (CV%)	35	5.6	21	35	27	42
ω_3	IIV in Ka (CV%)	145	5.1	21	144	131	157
ω_4	IIV in Fm (CV%)	36	3.7	4.4	36	32	40
ω_5	IIV in V3 (CV%)	28	7.6	21	28	20	35
ω_6	IIV in ALAG (CV%)	56	3.7	27	56	51	60
Residual variability							
σ_1	Selumetinib proportional error	0.16	3.5	9.2	0.17	0.14	0.19
σ_2	N-desmethyl selumetinib proportional error	0.12	2.3	8.8	0.12	0.11	0.14
σ_3	[¹⁴ C]-selumetinib proportional error	0.19	11.0	4.3	0.18	0.10	0.27

^a RSE (%) for parameters were obtained through the covariance step in NONMEM (the hessian evaluated at the final parameter estimates, MATRIX=R).

Reviewer's comment: The Applicant's population PK model is acceptable. The recommended BSA-based dosing is supported by the clinically relevant BSA effect on PK.

19.4.4. Physiologically based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report, entitled "PBPK Modeling Report-MS-02" to predict the effects of 1) CYP3A inhibitors (erythromycin and diltiazem), 2) a CYP2C19 inhibitor (fluoxetine) and 3) CYP3A inducers (efavirenz and dexamethasone) on the PK of selumetinib.

The Division of Pharmacometrics has reviewed the submitted PBPK reports, supporting modeling files, and the Applicant's responses to FDA's information requests (IRs) submitted on October 30, 2019 and December 19, 2019. FDA reviewer conducted additional PBPK analyses and concluded the followings.

- The PBPK analyses describe the observed selumetinib PK profiles following a single intravenous infusion (0.08 mg, 0.25hr), a single oral dose administration (25 and 75 mg) and multiple oral dose administration (25, 50, and 75 mg, bid).
- The analyses are adequate to predict the effect of erythromycin and diltiazem on the PK of selumetinib in healthy subjects. The model predicts an approximate 40% or 30% increase in selumetinib AUC when coadministered with erythromycin or diltiazem, respectively.
- The analyses are adequate to predict the effect of efavirenz and dexamethasone on the PK of selumetinib in healthy subjects. The model predicts an approximate 40% reduction in selumetinib AUC when coadministered with efavirenz, while no significant change in selumetinib exposure was predicted when coadministered with dexamethasone.

Applicant's PBPK Modeling Effort

PBPK software

Simcyp V17 (Simcyp Ltd, UK) was used to develop the Applicant's selumetinib PBPK models and predicted the effects of CYP3A inhibitors (erythromycin and diltiazem), a CYP2C19 inhibitor (fluoxetine) and CYP3A inducers (efavirenz and dexamethasone) on the PK of selumetinib.

Model development

Selumetinib

The first order absorption model was used. In vitro and in silico dataset (such as MDCKII assay) were used to predict the effective passive intestinal permeability (P_{eff}), fraction absorbed (f_a), absorption rate constant (k_a) and nominal flow in gut (Q_{gut}). The predicted P_{eff} , f_a and Q_{gut} were 6.88×10^{-4} cm/s, 0.99 and 15.0 L/h, respectively. The Applicant assigned the f_{gut} (unbound fraction in enterocytes) value to be 1.0. A minimal PBPK model with a single adjusting compartment (SAC) was applied to capture the distribution phase of selumetinib PK profile. For the SAC compartment, inter-compartment clearance (Q , 8L/h) was predicted using Pop PK model and the apparent volume associated with the SAC (V_{sac} , 1 L/kg) was estimated based on

the observed selumetinib C_{max} and PK profile (Study 83). The predicted volume of distribution (V_{ss}) was 1.37 L/kg using the method 2 in Simcyp (Rodgers and Rowland method).

The Applicant reported the average oral clearance of selumetinib (CL_{po}) is 19.6 L/hour based on 9 clinical studies. The percentages of selumetinib metabolized by CYP3A4 and CYP2C19 were assigned as 25% and 15% according to the DDI study with itraconazole and fluconazole, respectively. The intrinsic clearance values of 0.568 and 3.335 µl/min/pmol were estimated for CYP3A4 and CYP2C19, respectively. The rest of the metabolism was assigned as the additional human liver microsome clearance (186.8 µl/min/mg). Renal elimination was not considered in the model because less than 1% of the dose eliminated as unchanged drug in urine (Study YAU169).

In-vitro data showed that selumetinib is not a perpetrator of enzyme- or transporter- mediated pathways at clinically relevant concentrations of selumetinib. Selumetinib is a substrate of P-gp with low affinity. P-gp mediated drug efflux was not incorporated in the selumetinib PBPK model.

Victim drug models

The default PBPK models of erythromycin, diltiazem, fluoxetine, efavirenz, and dexamethasone in SimCYP were used without any modification for DDI prediction.

FDA's assessment

- The mass balance study showed that unchanged selumetinib accounted for about 20% of the dose in the feces. However, the fa value for selumetinib in Applicant's model was 0.99 and no biliary secretion was considered in the model. An information request was issued requesting the Applicant to provide justification for a fa value of 0.99 derived in the model.
- Selumetinib is highly bound to plasma protein with an unbound fraction of 0.016 in plasma. The fugut was set to 1 in Applicant's model which may increase the selumetinib extraction across the intestine, and thus the estimated fmCYP3A would be lower than that estimated using a model with a lower fugut. An information request was issued requesting the Applicant to evaluate the effect of fugut on the predicted selumetinib PK and exposure change of selumetinib with itraconazole, fluconazole or rifampicin.
- The Applicant's estimated fmCYP3A4 and fmCYP2C19 for selumetinib were 0.25 and 0.15 according to the DDI study results with itraconazole and fluconazole, respectively. An information request was issued to suggest the Applicant to re-estimate the fmCYP3A4 and fmCYP2C19 by considering the AUC metabolite (N-desmethyl selumetinib) to parent drug ratio.
- An information request was issued requesting the Applicant to verify model with selumetinib PK data following both intravenous (Study D1532C00080) and oral administration.

- In vitro study indicated that selumetinib is a P-gp substrate with a low affinity. P-gp mediated drug efflux was not incorporated in the selumetinib PBPK model. An information request was issued requesting the Applicant to provide justification or the simulated result to indicate the effect of P-gp is negligible.

Applicant's response to FDA's IR and FDA's assessment

- Fraction absorbed (fa)

In the response to the FDA's Information Request, the Applicant stated that a fa value of 0.99 was assigned according to the preclinical and clinical studies as summarized below:

There is no glucuronide conjugate in rat feces after intravenous or oral administration of selumetinib, but the glucuronide conjugate is the major component in the bile following bile-duct cannulation in rats. This result suggests that the glucuronide conjugate is likely converted back to the parent drug in the GI tract, which is thereafter being reabsorbed and return to the systemic circulation. In human, 20% of unchanged selumetinib was excreted in feces while no direct glucuronide conjugates were detected. The Applicant concluded that the unchanged selumetinib observed in human feces may be from the deconjugation of the glucuronide conjugates in GI tract, thus a high fa value (0.99) was assigned in the Applicant's PBPK model.

Reviewer note: it remains unclear how much unchanged selumetinib in feces was due to the deconjugation of the glucuronide conjugate and how much was from the drug remaining unabsorbed in the GI tract after oral administration. Thus, the FDA' reviewer discussed the scenario where selumetinib absorption was not complete. Refer to 'FDA's reviewer's analysis'.

- Unbound fraction in enterocyte (fugut)

Fugut value is not routinely measured, and it is often assigned by the modeler using different assumption or in silico methods. When a smaller fugut value was assigned in the model, more drug would pass through the gut wall without metabolism. Therefore, the estimated fmCYP would be different using different fugut values for those enzymes which are present in both intestine and liver. In the response to the FDA's Information Request, the Applicant discussed a scenario where fugut was assumed to equal fup (0.016). FDA' reviewer conducted additional analysis to evaluate the alternative modeling approaches to assign fugut value(s) in the model. Refer to 'FDA's reviewer's analysis'.

- fmCYP2C19

In the response to the FDA's Information Request, the Applicant re-assigned fmCYP2C19 (0.07) to the value reported for the AUC ratio of metabolite (N-desmethyl selumetinib) to parent drug in plasma (0.07). It was assumed that CYP2C19 is the only enzyme responsible

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for the formation of N-desmethyl selumetinib and both selumetinib and N-desmethyl selumetinib have similar elimination rates.

o P-gp

In the response to the FDA’s Information Request, the Applicant developed a full PBPK model with ADAM absorption and incorporated P-gp kinetics in the intestine and liver. The in vitro estimated P-gp Jmax (9.9 pmol/min) and Km (15.8 μM) values was used as initial values in the model development and a sensitivity analysis was performed. The sensitivity analysis suggests that the impact of P-gp on the PK of selumetinib is likely to be negligible. The Applicant’s modeling analysis is adequate to assess the impact of P-gp on selumetinib PK.

FDA reviewer’s analysis

Given the limitations identified in Applicant’s modeling approach, the FDA’s reviewer further refined the model by re-optimizing the model parameters to better capture the clinical DDI study results with itraconazole, fluconazole, and rifampicin.

The model refinement was based on the liver availability (Fh) and absolute bioavailability (F) . Fh can be calculated from the following equation,

$$F_h = 1 - E_h = 1 - \frac{CL_{h,p}}{Q_h * B/P}$$

Where CLh,p is the plasma clearance of selumetinib following intravenous administration which can be obtained from Study 80 (11.4 L/h); Qh is the blood flow in the hepatic portal vein (90 L/h); B/P is the concentration ratio of drug in blood to plasma (0.625); Eh is the fraction of the drug that is extracted by the liver. The Fh was calculated to be 0.797. The observed absolute bioavailability in Study 80 was 0.621. Thus, the lowest possible fa is 0.8 given a F value of 0.621 and Fh is around 0.8.

Table 68 Parameter values (fa, Fg, Fh, fugut, fmCYP3A4 and fmCYP2C19) implemented in Model 1 and Model 2 and the simulated and observed Cmax and AUC ratios in the presence and absence of a CYP modulator

Model	Inhibitor	fa	fg	Fh	F	fugut	fmCYP3A4	fmCYP2C19	Simulated		Observed		Sources
									CmaxR	AUCR	CmaxR	AUCR	
Model 1	Itraconazole	0.84	0.91	0.77	0.60	0.302	0.29	0.075	1.19	1.48	1.19	1.49	Study 83
	Fluconazole		0.91		0.60				1.20	1.54	1.26	1.53	
	Rifampicin		0.95		0.61				0.60	0.39	0.74	0.49	Study 85
Model 2	Itraconazole	0.98	0.83	0.78	0.64	1.00	0.25	0.075	1.21	1.47	1.19	1.49	Study 83
	Fluconazole		0.82		0.63				1.22	1.53	1.26	1.53	
	Rifampicin		0.80		0.61				0.49	0.32	0.74	0.49	Study 85

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Two scenarios were discussed regarding the different f_a values:

- 1) **Model 1:** assume complete oral absorption ($f_a = 1$); and
- 2) **Model 2:** assume incomplete oral absorption ($f_a \sim 0.8$)

As shown in Table 77, F_g can be calculated based on the known F , F_h , and the assumed f_a . The corresponding $f_{mCYP3A4}$, $f_{mCYP2C19}$ in Model 1 and Model 2 can be derived based on the clinical DDI result with itraconazole and fluconazole. The AUC ratio of metabolite (N-desmethyl selumetinib) to parent drug was also considered. Both models were verified with the observed selumetinib PK following intravenous and oral administration (Table 74). It should be noted that the model predicted DDI of selumetinib with rifampicin was overestimated as compared to the clinical observed results (AUCR: 0.39 vs 0.49) (Table 76). Rifampicin is a pleiotropic inducer. It may interact with multiple pathways which could affect the exposure of selumetinib, whereas the rifampicin model used in this analysis may not account for all the interaction mechanisms. The model verification results were shown in Figure 24 and Table 78. After model verification with the clinical PK and DDI data, Model 1 and Model 2 were applied to assess the DDI potential of selumetinib as a victim with CYP3A4 and CYP2C19 modulators.

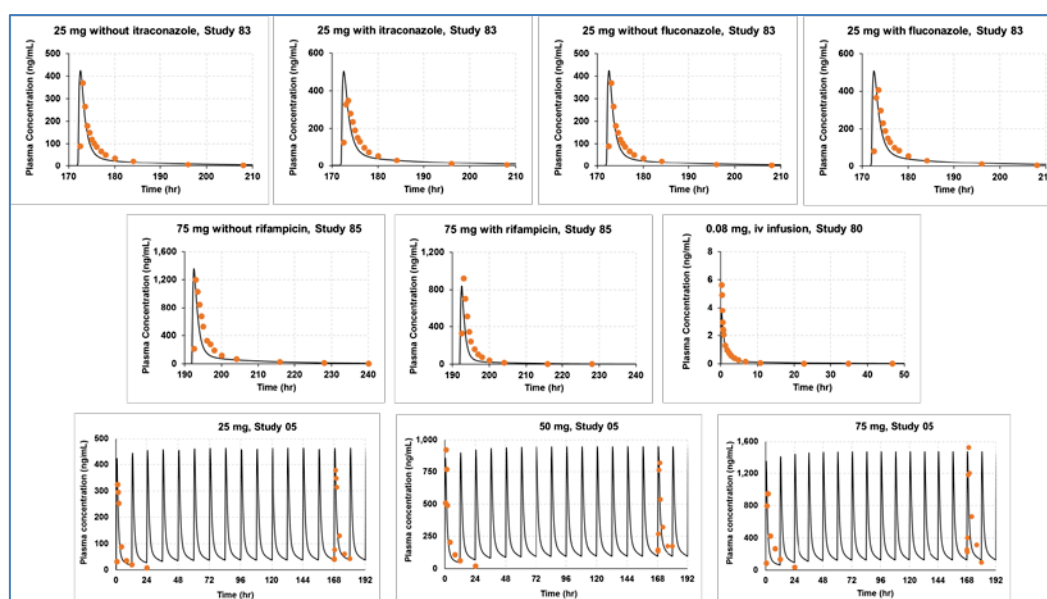


Figure 24 Observed (dots or circles) and simulated (lines) selumetinib plasma concentration-time profiles following a single intravenous infusion (0.08 mg, 0.25 hr) or a single dose (25 or 75 mg) administration in healthy subjects in the presence and absence of itraconazole, fluconazole or rifampicin, or multiple dose administration (25, 50 and 75mg, bid) in patients with advanced solid malignancies. The selumetinib PK profiles were simulated using Model 1. The model

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verification results were similar between Model 1 and Model 2 and only results from Model 1 simulation was shown.

Table 69 Observed and simulated selumetinib geometric mean PK parameters using Model 1 and Model 2 following a single intravenous infusion (0.08 mg, 0.25 hr) or a single dose (25 or 75 mg) administration in healthy subjects in the presence and absence of itraconazole, fluconazole or rifampicin, or multiple dose administration (25, 50 and 75mg, bid) in patients with advanced solid malignancies.

Model 1	Cmax (ng/mL)			AUC (ng*h/mL)			Cmax ratio		AUC ratio		Sources
	Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	Obs.	Pred.	
IV infusion 0.08 mg, 0.25 hr	5.87	3.34	0.57	7.05	6.44	0.91					Study 80
Oral, 25 mg bid, day 1	369	414	1.12	1114	962	0.86					Study 05
Oral, 25 mg bid, day 8	457	454	0.99	1515	1269	0.83					
Oral, 50 mg bid, day 1	1036	815	0.79	2584	1965	0.76					
Oral, 50 mg bid, day 8	987	901	0.91	3381	2653	0.78					
Oral, 75 mg bid, day 1	1207	1264	1.05	4901	2956	0.60					
Oral, 75 mg bid, day 8	1439	1385	0.96	5448	3891	0.71					
25 mg w/o itraconazole	409	397	0.97	1180	1113	0.94	1.19	1.19	1.49	1.48	Study 83
25 mg with itraconazole	484	472	0.98	1760	1644	0.93					
25 mg w/o fluconazole	409	398	0.97	1180	1126	0.95	1.26	1.20	1.53	1.54	
25 mg with fluconazole	509	477	0.94	1770	1737	0.98					
75 mg w/o rifampicin	1440	1282	0.89	4480	3593	0.80	0.74	0.60	0.49	0.39	Study 85
75 mg with rifampicin	1070	770	0.72	2200	1389	0.63					

Notes: Number of patients in 25, 50 and 75 mg dose cohorts in Study 05 were 6, 8 and 7, respectively.
Study 05 was conducted in patients with advance solid malignancies. Study 80, 83 and 85 were conducted in healthy subjects. Simulations were performed using Model 1 and Model 2 in healthy subjects.

Model 2	Cmax (ng/mL)			AUC (ng*h/mL)			Cmax ratio		AUC ratio		Sources
	Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	R _{Pred/Obs}	Obs.	Pred.	Obs.	Pred.	
IV infusion 0.08 mg, 0.25 hr	5.87	3.42	0.58	7.05	6.78	0.96					Study 80

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Oral, 25 mg bid, day 1	369	391	1.06	1114	1052	0.94					Study 05	
Oral, 25 mg bid, day 8	457	433	0.95	1515	1399	0.92						
Oral, 50 mg bid, day 1	1036	774	0.75	2584	2161	0.84						
Oral, 50 mg bid, day 8	987	869	0.88	3381	2950	0.87						
Oral, 75 mg bid, day 1	1207	1130	0.94	4901	3095	0.63						
Oral, 75 mg bid, day 8	1439	1252	0.87	5448	4098	0.75						
25 mg w/o itraconazole	409	383	0.94	1180	1327	1.12	1.19	1.21	1.49	1.47	Study 83	
25 mg with itraconazole	484	465	0.96	1760	1951	1.11						
25 mg w/o fluconazole	409	378	0.92	1180	1279	1.08	1.26	1.22	1.53	1.53		
25 mg with fluconazole	509	461	0.91	1770	1952	1.10						
75 mg w/o rifampicin	1440	1166	0.81	4480	3881	0.87	0.74	0.51	0.49	0.34		Study 85
75 mg with rifampicin	1070	600	0.56	2200	1338	0.61						

PBPK model application

The developed PBPK models were used to simulate the DDI for selumetinib in the following scenarios.

- To predict the effect of erythromycin (a moderate CYP3A inhibitor) and diltiazem (a moderate CYP3A inhibitor) on the PK of selumetinib in healthy subjects.
- To predict the effect of fluoxetine (a strong CYP2C19 inhibitor) on the PK of selumetinib in healthy subjects.
- To predict the effect of efavirenz (a moderate CYP3A inducer) and dexamethasone (a weak CYP3A inducer) on the PK of selumetinib in healthy subjects.

Results

1. Can FDA refined selumetinib PBPK models describe selumetinib PK in healthy subjects?

Yes. The refined selumetinib models (Model 1 and Model 2) were able to capture the observed selumetinib PK following a single intravenous infusion (0.08 mg, 0.25hr) and a single oral dose administration (25 and 75mg) in healthy subjects and multiple dose administration (25, 50 and 75mg, bid) in patients with advanced solid malignancies. The model predicted selumetinib bioavailability after oral dosing is similar to the observed absolute bioavailability (0.62). The potential effect of uncertainty associated with the fraction absorbed (fa) on the selumetinib PK prediction was also explored using Model 1 and 2. No significant difference was found in the selumetinib PK prediction using Model 1 and Model 2 (Table 77 and Table 78).

2. Can FDA refined selumetinib PBPK models predict the effect of erythromycin (a moderate CYP3A inhibitor) and diltiazem (a moderate CYP3A inhibitor) on the PK of selumetinib in healthy subjects?

Yes. The models (Model 1 and Model 2) are adequate to predict the effect of erythromycin and diltiazem on the PK of selumetinib in healthy subjects. About 40% or 30% increase in selumetinib AUC were predicted with erythromycin or diltiazem, respectively (Table 79).

Table 70 Model predicted selumetinib Cmax and AUC ratios in the presence and absence of a CYP3A modulator

CYP3A modulator	Model 1		Model 2	
	CmaxR	AUCR	CmaxR	AUCR
Erythromycin (a moderate CYP3A inhibitor), 500 mg, TID	1.16	1.39	1.17	1.35
Diltiazem (a moderate CYP3A inhibitor), 60 mg, TID	1.12	1.28	1.14	1.28
Efavirenz (a moderate CYP3A4 inducer), 600 mg, QD	0.79	0.56	0.80	0.61
Dexamethasone (a weak CYP3A4 inducer), 8 mg, QD	1.00	1.00	1.00	1.00

3. Can FDA refined selumetinib PBPK models predict the effect of fluoxetine (a strong CYP2C19 inhibitor) on the PK of selumetinib in healthy subjects?

The predicted selumetinib AUC was increased about 35% with fluoxetine. Based on the model analysis, about 10% increase in the selumetinib AUC can be potentially attributed to the fluoxetine mediated CYP2C19 inhibition, whereas about 20% increase in the selumetinib AUC was due to the fluoxetine mediated CYP3A4 inhibition.

The default fluoxetine PBPK model in SimCYP incorporated both fluoxetine and its metabolite norfluoxetine mediated competitive inhibition and time dependent inhibition of CYP3A4 based on in vitro study results^{1,2} and model was verified using clinical DDI study results³. The clinical DDI study⁴ showed that alprazolam (a moderate sensitive CYP3A4 substrate) AUC was increased by 32% after co-administration of fluoxetine. However, Sager et al⁵ recently reported that fluoxetine had no effect on midazolam AUC (a sensitive CYP3A4 substrate) in vivo. The magnitude of fluoxetine mediated CYP3A4 inhibition remained to be confirmed in future studies. Therefore, the simulated DDI effects of fluoxetine on selumetinib exposure was not used to support the dosing recommendation.

4. Can FDA refined selumetinib PBPK models predict the effect of efavirenz (a moderate CYP3A inducer) and dexamethasone (a CYP3A inducer) on the PK of selumetinib in healthy subjects?

Yes. The models (Model 1 and 2) are adequate to predict the effect of efavirenz and dexamethasone on the PK of selumetinib in healthy subjects. About 40% reduction in selumetinib AUC was predicted with efavirenz. The selumetinib exposure would not be expected to be significantly affected by concomitant dexamethasone (Table 78).

Conclusion:

The Applicant's selumetinib model was refined by the FDA reviewer to explore the alternative PBPK parameters (such as fmCYPs and fa) and their impacts on DDI prediction. The selumetinib PBPK model described the observed DDI of selumetinib with itraconazole (a strong CYP3A4 inhibitor) and fluconazole (a strong CYP2C19 inhibitor and a moderate CYP3A4 inhibitor). The PBPK analyses are adequate to predict the effect of various CYP3A and CYP2C19 modulators on the selumetinib PK. (b) (4)

¹ Mayhew BS, Jones DR, Hall SD. An in vitro model for predicting in vivo inhibition of cytochrome P450 3A4 by metabolic intermediate complex formation. Drug Metab Dispos. 2000 Sep;28(9):1031-7.

² Albaugh DR, Fullenwider CL, Fisher MB, Hutzler JM. Time-dependent inhibition and estimation of CYP3A clinical pharmacokinetic drug-drug interactions using plated human cell systems. Drug Metab Dispos. 2012 Jul;40(7):1336-44.

³ Hall J, Naranjo CA, Sproule BA, Herrmann N. Pharmacokinetic and pharmacodynamic evaluation of the inhibition of alprazolam by citalopram and fluoxetine. J Clin Psychopharmacol. 2003 Aug;23(4):349-57.

⁴ Hall J, Naranjo CA, Sproule BA, Herrmann N. Pharmacokinetic and pharmacodynamic evaluation of the inhibition of alprazolam by citalopram and fluoxetine. J Clin Psychopharmacol. 2003 Aug;23(4):349-57.

⁵ Sager JE, Lutz JD, Foti RS, Davis C, Kunze KL, Isoherranen N. Fluoxetine- and norfluoxetine-mediated complex drug-drug interactions: in vitro to in vivo correlation of effects on CYP2D6, CYP2C19, and CYP3A4. Clin Pharmacol Ther. 2014 Jun;95(6):653-62.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

There were no additional safety analyses performed by FDA that have not already been discussed under the safety sections of this application.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	G. Sachia Khasar	OOD/DHOT	Sections: Nonclinical excluding carcinogenicity	Select one: ☒ Authored ☐ Approved
	Signature: Gabriel S. Khasar -S Digitally signed by Gabriel S. Khasar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=200095653, cn=Gabriel S. Khasar -S Date: 2020.04.06 11:58:40 -04'00'			
Nonclinical Reviewer	M. Anwar Goheer	OOD/DHOT	Sections: Carcinogenicity	Select one: ☒ Authored ☐ Approved
	Signature: Mohammad A. Goheer -S Digitally signed by Mohammad A. Goheer -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300045035, cn=Mohammad A. Goheer -S Date: 2020.04.07 13:14:02 -04'00'			
Nonclinical Team Leader	Whitney S. Helms	OOD/DHOT	Sections: Nonclinical	Select one: ☐ Authored ☒ Approved
	Signature: Whitney S. Helms -S Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.04.06 11:44:31 -04'00'			
Nonclinical Team Division Director	John K. Leighton	OOD/DHOT	Sections: Nonclinical	Select one: ☐ Authored ☒ Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.04.06 12:28:42 -04'00'			
Clinical Pharmacology Reviewer	Lili Pan	OCP/Division of Cancer Pharmacology II	Sections: 6, 19.4.1, 19.4.2	Select one: ☒ Authored ☐ Approved
	Signature: Lili Pan -S Digitally signed by Lili Pan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lili Pan -S, 0.9.2342.19200300.100.1.1=2001832999 Date: 2020.04.06 09:28:15 -04'00'			
Clinical Pharmacology Team Leader	Ruby Leong	OCP/Division of Cancer Pharmacology I	Sections: 6, 19.4.1, 19.4.2	Select one: ☐ Authored ☒ Approved
	Signature: Ruby Leong -S Digitally signed by Ruby Leong -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ruby Leong -S, 0.9.2342.19200300.100.1.1=2000548953 Date: 2020.04.07 13:28:56 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/Division of Cancer Pharmacology II	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.04.07 14:35:46 -04'00'			
Pharmacometrics Reviewer	Yuan Xu	OCP/DPM	Sections: 6, 19.4.3	Select one: ☐ Authored ☒ Approved
	Signature: Yuan Xu -S Digitally signed by Yuan Xu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan Xu -S, 0.9.2342.19200300.100.1.1=2001686060 Date: 2020.04.06 10:26:39 -04'00'			
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections: 6, 19.4.3	Select one: ☒ Authored ☒ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.04.06 09:42:04 -04'00'			
PBPK Reviewer	Jianghong Fan	OCP/Division of Pharmacometrics	Sections: 6, 19.4.4	Select one: ☒ Authored ☐ Approved
	Signature: Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2020.04.06 10:35:09 -04'00'			
PBPK Team Leader	Yuching Yang	OCP/Division of Pharmacometrics	Section: 6, 19.4.4	Select one: ☐ Authored ☒ Approved
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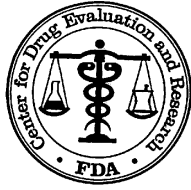
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION CARCINOGENICITY STUDIES

NDA/BLA #: NDA 213756/SN-0001

Drug Name: Selumetinib Capsule (AZD6244)

Indication(s): Treatment for pediatric patients, aged 3 years and above, with neurofibromatosis-1 (NF1) and symptomatic, inoperable plexiform neurofibroma (PN).

Applicant: AstraZeneca Pharmaceuticals LP
1800 Concord Pike, Wilmington, Delaware, 19803, USA

Laboratory: [REDACTED] (b) (4)

Date(s): Received 10/30/2019

Documents Reviewed: Studies 501094-3855cr (rats) 20086561-0994cm (mice) were submitted on 7/26/2019 (via NDA 213756/SN0001) and the electronic tumor.xpt files were submitted at the same time.

Review Priority: Priority Review

Biometrics Division: Division of Biometrics VI

Statistical Reviewer: Feng Zhou

Concurring Reviewers: Karl Lin, Ph. D., Team Leader

Medical Division: Division of Division of Oncology Products 2 (CDER/OND/OHOP/DOPII)

Nonclinical Team: Anwar Goheer, Ph.D; Whitney Helms, Ph.D

Project Manager: Sharon Sickafuse

Keywords: Carcinogenicity, Dose response

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1 Summary

This review evaluates statistically the data of the 2-year oral carcinogenicity study in Han Wistar CRL: WI(HAN) rats and 6-months oral carcinogenicity study in CByB6F1/TgrasH2 transgenic mice. The review analyzes the dose-response relationship of tumor incidences and mortality (including tumor-related mortality). From the statistical point of view, the review concludes that AZD6244 had no effect on survival. The tumor analysis showed no statistically significant dose-response relationship or pairwise increase in tumor incidence for either sex in rats or mice.

Rat Study: Rats (50/sex/dose) were dosed by oral gavage with AZD6244 daily for up to 104 weeks. The respective AZD6244 dose in the water control (WC), vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 0, 0.25, 0.8, or 2.5 mg/kg/day in male and 0, 0, 0.1, 0.3, or 1 mg/kg/day in females. The treatments for all rats were terminated at Week 104.

The survival analyses didn't show any statistically significant dose response relationship or pairwise difference in mortality in males and females. The respective survival rates in the WC, VC, LD, MD, or HD groups at the time they were terminated were 64%, 60%, 70%, 66%, or 70% in males and 76%, 72%, 78%, 76%, or 72% in females.

The tumor analysis showed that there were no statistically significant positive dose-response relationships or statistically significant pairwise increase against the vehicle control or water control for any tumor types tested.

Mouse Study: Mice (25/sex/dose) were dosed by oral gavage with AZD6244 daily for up to 26 weeks. The respective AZD6244 doses in the vehicle control (VC), low (LD), mid (MD), and high-dose (HD) groups were 0, 6, 16, or 50 mg/kg/day in males and females. The 50 mg/kg/day level was reduced to 30 mg/kg/day beginning on Week 19 due to excessive mortality. Also, a positive control group consisting of 15 males and 15 females was dosed intraperitoneally with 7.5 mg/mL N-Nitrosomethylurea (NMU) in citrate-buffered saline on Day 1 only. The treatments for male mice and female mice were terminated at Weeks 27, respectively.

The survival analyses showed a statistically significant dose response relationship in male mice only. Mortalities in male HD group and positive control groups for male and female were significantly higher than that of the vehicle or water control group. The respective survival rates in the WC, VC, LD, MD, HD, or PC groups at the time they were terminated were 100%, 100%, 100%, 100%, 88%, or 13% in males and 100%, 100%, 100%, 96%, 100%, or 20% in females.

The tumor analysis showed that no AZD6244-related effects on the incidence of neoplastic findings were noted for male and female mice. The incidence rates of tumor types of malignant lymphoma in hemolymphoreticular tissue, papilloma in skin and stomach in male and female mice were statistically significant higher in the positive control than those in the vehicle control.

2 Background

Selumetinib (AZD6244) is a potent, selective, oral, inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2) that is not competitive with respect to adenosine triphosphate (ATP). This application is for the use of selumetinib as an oral treatment for paediatric patients aged 3 years and above, with neurofibromatosis type 1 (NF1) and symptomatic, inoperable plexiform neurofibromas (PN). AstraZeneca (the sponsor) submitted the nonclinical studies 501094-3855cr: "A 104-week oral carcinogenicity study in Wistar rats" and 20086561-0994cm: "A 26-week oral carcinogenicity study in mice" via submission NDA 213756/SN-0001. The electronic tumor.xpt files were submitted at the same time.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. The dose unit "mg/kg/day" will be referred to "mkd" in the tumor tables. Results of this review have been discussed with the nonclinical team.

3 Rat Study- 501094-3855cr

Study Report: 501094-3855cr-report.pdf (statistical report on page 3919)

SAS data: tumor.xpt

This study was conducted to evaluate the carcinogenic potential of the test article, AZD6244, after once daily oral gavage administration to male and female Han Wistar CRL: WI(HAN) rats for up to 104 consecutive weeks. The test material was administered at doses of 0.25, 0.8, or 2.5 mg/kg/day for males and 0.1, 0.3, or 1 mg/kg/day for females. This review refers these dose groups as the low (LD), mid (MD), or high (HD) dose groups, respectively. Two groups of the same size were used as controls. One control group was dosed with Milli-Q water and the other was dosed with the vehicle, 10% ethanol, 30% PEG 400 and 60% Phosal 50. This review refers these two groups as vehicle control (VC) and water control (WC). There were 50 rats/sex/dose in the main study. All rats were terminated at Week 104.

Pairwise comparisons were performed against Vehicle Control. The following pairwise comparisons were performed: VC group vs WC group and VC group vs dosed groups.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test¹². Any animal with accidental injury that caused death or unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test was significant ($p < 0.05$) and there were more than two

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groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: There were no statistically significant differences (Kaplan-Meier) in mortality between any of each of the water control group and the treated groups and the vehicle control for males or females.

3.1.2 Tumor Data Analysis

Neoplastic findings classified as fatal and incidental were processed using the Peto death rate method and the Peto prevalence method, respectively. The processing of incidental tumors was done by creating a single separate interval for the time following the experimental period (terminal sacrifice period) and by dividing the experimental period into the following fixed intervals [FDA's draft Guidance for industry, 2001]: weeks 1-52, weeks 53-78, weeks 79-92, and over week 92, and over week 92. Using the derived outcomes from the processing of both fatal and incidental tumors, a test statistic was built to perform a global survival-adjusted trend test on tumor data observed in a "mortality dependent" context [Peto et al, 1980].

All p-values are reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (levels of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%) The evaluation criteria from the FDA are given in Table F (FDA).

Table F. Evaluation Criteria for Common and Rare Tumors	
Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Sponsor's concluded results: There were no neoplastic or proliferative findings attributable to administration of AZD6244.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 7/26/2019 via NDA 213756/SN0001.

3.2.1 Survival Analysis

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response

relationship was tested using the likelihood ratio test and the homogeneity of survival distributions were tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of death that occurred prior to termination of the group were 20 (40%), 15 (30%), 12 (34%), 15 (30%), or 18 (36%) in male rats and 14 (28%), 11 (22%), 12 (24%), 14 (28%), or 12 (24%) in female rats in the VC, LD, MD, HD, or WC groups, respectively. The survival analyses didn't show any statistically significant dose response relationship in mortality in males and females.

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k < 1$. The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104-week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively. A rare tumor is defined as one in which the tumor rate is less than 1% in the vehicle control group.

The tumor rates and the p-values of the tested tumor types are listed in Tables 5A and 5B in the appendix for male and female rats, respectively.

Reviewer's findings: There were no AZD6244-related effects on the incidence of neoplastic findings were noted.

4 Mouse Study- 20086561-0994cm

Study Report: 20086561-0994cm-report.pdf (statistical report on page 1420)

SAS data: tumor.xpt

This study was conducted to evaluate the carcinogenic potential of the test article, AZD6244, after twice daily oral gavage administration to male and female CByB6F1/TgrasH2 transgenic mice for up to 26 consecutive weeks. The test material was administered at doses of 6, 16, or 50/30 mg/kg/day for male and female mice. This review refers these dose groups as the low (LD), mid (MD), and high (HD) dose groups, respectively. The 50 mg/kg/day level was reduced to 30 mg/kg/day beginning on Week 19 due to excessive mortality. There were 25 mice/sex/dose in the main study. Similarly constituted control groups were treated with reverse osmosis deionized (RODI) water or the control article alone (10% ethanol, 30% PEG 400, and 60% Phosal 50 PG). Also, a positive control group consisting of 15 males and 15 females was dosed intraperitoneally with 7.5 mg/mL N-Nitrosomethylurea (NMU) in citrate-buffered saline on Day 1 only. This review refers these controls as water control (WC), vehicle control (VC) or positive control (PC).

Table 2.1 Study Design

Protocol Group	Dose Material	Males		Females	
		Dose Level per Dose (mg/kg)	Number of Animals Examined ^a	Dose Level per Dose (mg/kg)	Number of Animals Examined ^a
1	RODI Water	0	25	0	25
2	Control Article	0	25	0	25
3	AZD6244	3	25	3	25
4	AZD6244	8	25	8	25
5	AZD6244	25/15 ^b	25	25/15 ^b	25

a- number of animals for which at least one organ was examined
b- dose level was reduced to 15/mg/kg/dose beginning on Week 19, Day 130.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: There were no statistically significant findings among males or females for survival rates.

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study.

Sponsor's findings: There were no statistically significant tumor findings among males and females.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 7/26/2019 via NDA 213756/SN0001.

4.2.1 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death that occurred prior to termination of the group were 0, 0, 0, 0, 3 (12%) or 13 (87%) in male mice and 0, 0, 0, 1 (4%), 0, or 12 (80%) in female mice in the WC, VC, LD, MD, HD, or PC groups, respectively. The survival analyses show a statistically significant dose response relationship in mortality in males only. Mortalities in male HD group and positive control for male and female group were significantly higher than that of the vehicle or water control group.

4.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the water control group and the vehicle control group separately with each of the treated groups, the water control group, and the positive control group using the same method that was used for the rat study. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, and 6B in the appendix for male and female mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 for pairwise comparisons of vehicle control and positive control.

Tumor Types with P-Values ≤ 0.05 for Pairwise Comparisons of Vehicle Control and Positive Control in Mice

Sex	Organ name	Tumor name	0 mg Vehicle (C) P - Trend	0 mg Water (WC) P - C vs. WC	75 mg Positive (PC) P - C vs. PC
Male	Hemolymphoreticular Tissue	Lymphoma,	0/25 (25)	0/25 (24)	10/15 (13)
		Malignant	NC	NC	0.0000 **
	Skin	Papilloma	0/25 (25)	0/25 (24)	5/15 (9)
			NC	NC	0.0005 **
Stomach	Papilloma	0/25 (25)	0/25 (24)	8/15 (11)	

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Sex	Organ name	Tumor name	0 mg Vehicle (C) P - Trend	0 mg Water (WC) P - C vs. WC	75 mg Positive (PC) P - C vs. PC
			0.2268	NC	0.0000 **
Female	Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (25) NC	0/25 (24) NC	11/15 (14) 0.0000 **
	Skin	Papilloma	0/25 (25) NC	0/25 (25) NC	6/15 (10) 0.0001 **
		Squamous Cell Carcinoma	0/25 (25) NC	2/25 (25) 0.2449	10/15 (12) 0.0000 **
	Stomach	Papilloma	1/25 (25) 0.8093	0/25 (24) NC	11/14 (12) 0.0000 **

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Based on the criteria of adjustment for multiple testing discussed above, there were no AZD6244-related effects on the incidence of neoplastic findings were noted. The tumor types listed in the table above had statistically significant pairwise increases in tumor incidence in the positive control when compared with the vehicle control group.

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6

cc:

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5 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

Week / Type of Death	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52			2	4.00	2	4.00			1	2.00
53 - 78	7	14.00	7	18.00	2	8.00	7	14.00	2	6.00
79 - 96	9	32.00	2	22.00	8	24.00	6	26.00	9	24.00
97 - 104	4	40.00	4	30.00	5	34.00	2	30.00	6	36.00
Terminal sacrifice	30	60.00	35	70.00	33	66.00	35	70.00	32	64.00
Total	50		50		50		50		50	

Table 1B: Intercurrent Mortality Rate in Female Rats

Week / Type of Death	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	1	2.00			2	4.00	3	6.00	2	4.00
53 - 78	8	18.00	2	4.00	4	12.00	4	14.00	1	6.00
79 - 96	1	20.00	3	10.00	3	18.00	3	20.00	4	14.00
97 - 104	4	28.00	6	22.00	3	24.00	4	28.00	5	24.00
Terminal sacrifice	36	72.00	39	78.00	38	76.00	36	72.00	38	76.00
Total	50		50		50		50		50	

Table 2A: Intercurrent Mortality Rate in Male Mice

Week/ Type of Death	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control		Positive Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13							3	12.00			3	20.00
14-26											10	86.67
Accidental Death									1	4.00		
Terminal sacrifice	25	100.00	25	100.00	25	100.00	22	88.00	24	96.00	2	13.33
Total	25		25		25		25		25		15	

Table 2B: Intercurrent Mortality Rate in Female Mice

Week/ Type of Death	Vehicle Control		Low Dose		Mid Dose		High Dose		Water Control		Positive Control	
	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 13					1	4.00					1	6.67
14-26											11	80.00
Terminal sacrifice	25	100.00	25	100.00	24	96.00	25	100.00	25	100.00	3	20.00
Total	25		25		25		25		25		15	

Table 3A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. WC
Dose-Response (Likelihood Ratio)	0.5066	0.3996	0.6098	0.4210	NC
Homogeneity (Log-Rank)	0.7871	0.4046	0.6109	0.4260	NC

Table 3B: Intercurrent Mortality Comparison in Female Rats

Test	All Dose Groups	VC vs. Low	VC vs. Mid	VC vs. High	VC vs. WC
Dose-Response (Likelihood Ratio)	0.6021	0.5378	0.8257	0.7274	NC
Homogeneity (Log-Rank)	0.8642	0.5406	0.8258	0.7246	NC

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups Vehicle	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle vs. Water Control	Vehicle vs. Positive Control
Dose-Response (Likelihood Ratio)	0.0019	NC	NC	0.0107	NC	<.0001
Homogeneity (Log-Rank)	0.0071	NC	NC	0.0139	NC	<.0001

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups Vehicle	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle vs. Water Control	Vehicle vs. Positive Control
Dose-Response (Likelihood Ratio)	0.9330	NC	0.1383	NC	NC	<.0001
Homogeneity (Log-Rank)	0.2615	NC	0.1573	NC	NC	<.0001

Table 5A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats

Organ name	Tumor name	0 mkd Vehicle C P - Trend	0.25 mkd Low (L) P - VC vs. L	0.8 mkd Mid (M) P - VC vs. M	2.5 mkd High (H) P - VC vs. H	0 mkd Water C (WC) P - VC vs. WC	
Brain	Astrocytoma, Malignant	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	1/50 (44) 0.5176	
	Granular Cell Tumor, Benign	0/50 (41) 0.4281	2/50 (43) 0.2590	1/50 (43) 0.5119	1/50 (43) 0.5119	2/50 (44) 0.2650	
	Reticulosis, Malignant	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	0/50 (44) NC	
Epididymis	Mesothelioma, Malignant	2/50 (41) 0.9429	1/50 (43) 0.8881	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000	
	Eye	Schwannoma, Malignant	0/50 (41) 0.5059	1/50 (43) 0.5119	0/50 (43) NC	0/50 (43) NC	0/50 (44) NC
Gland, Adrenal	Cortical Adenoma	0/50 (41) 0.6952	2/50 (43) 0.2590	1/50 (43) 0.5119	0/50 (43) NC	1/50 (44) 0.5176	
	Pheochromocytoma, Benign	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	1/50 (44) 0.5176	
	Pheochromocytoma, Complex, Benign	0/50 (41) 0.4430	0/50 (43) NC	2/50 (43) 0.2590	0/50 (43) NC	0/50 (44) NC	
	Pheochromocytoma, Malignant	0/50 (41) 0.1916	0/50 (43) NC	1/50 (43) 0.5119	1/50 (43) 0.5119	0/50 (44) NC	
	Gland, Mammary	Fibroadenoma	1/49 (40) 0.7500	0/46 (40) 1.0000	0/45 (39) 1.0000	0/48 (41) 1.0000	0/50 (44) 1.0000

Organ name	Tumor name	0 mkd Vehicle C P - Trend	0.25 mkd Low (L) P - VC vs. L	0.8 mkd Mid (M) P - VC vs. M	2.5 mkd High (H) P - VC vs. H	0 mkd Water C (WC) P - VC vs. WC
Gland, Parathyroid	Adenoma	0/48 (39) 0.4937	1/47 (41) 0.5125	0/47 (40) NC	0/44 (38) NC	2/48 (42) 0.2657
Gland, Pituitary	Adenoma, Pars Distalis	16/49 (43) 0.9880	20/50 (48) 0.4136	15/50 (45) 0.7269	9/50 (45) 0.9791	13/50 (46) 0.8700
	Adenoma, Pars Intermedia	1/49 (40) 0.0770	0/50 (43) 1.0000	2/50 (44) 0.5361	3/50 (44) 0.3449	3/50 (44) 0.3449
	Carcinoma, Pars Distalis	0/49 (40) NC	0/50 (43) NC	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5238
Gland, Salivary, Parotid	Schwannoma, Malignant	0/49 (40) NC	0/49 (42) NC	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5238
Gland, Thyroid	C-Cell Adenoma	2/50 (41) 0.2428	1/49 (42) 0.8840	3/50 (43) 0.5229	3/50 (43) 0.5229	2/50 (44) 0.7183
	Follicular Cell Adenoma	0/50 (41) 0.8837	3/49 (42) 0.1249	0/50 (43) NC	0/50 (43) NC	2/50 (44) 0.2650
	Follicular Cell Carcinoma	0/50 (41) NC	0/49 (42) NC	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5176
Hemolymphoretic ular Tissue	Histiocytic Sarcoma	0/50 (41) NC	0/50 (43) NC	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5176
	Leukemia, Large Granular Lymphocytic	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000
	Lymphoma, Malignant	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	2/50 (44) 0.2650
Kidney	Adenoma	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	0/50 (44) NC
	Lipoma	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	0/50 (44) NC
	Liposarcoma	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	0/50 (44) NC
	Nephroblastoma, Malignant	0/50 (41) 0.2515	0/50 (43) NC	1/50 (44) 0.5176	0/50 (43) NC	0/50 (44) NC
Large Intestine, Rectum	Hemangioma	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	0/50 (44) NC
Liver	Hemangiosarcoma	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	0/50 (44) NC
Lymph Node, Mesenteric	Hemangioma	3/49 (40) 0.1234	5/50 (43) 0.3980	5/50 (43) 0.3980	7/48 (42) 0.1767	9/50 (45) 0.0888
	Hemangiosarcoma	1/49 (40) 0.6348	0/50 (43) 1.0000	1/50 (43) 0.7708	0/48 (42) 1.0000	1/50 (44) 0.7762
Pancreas	Adenoma	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	0/50 (44) NC
	Islet Cell Adenoma	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	1/50 (44) 0.7703
Skin	Basal Cell Tumor, Benign	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000
	Fibroma	2/50 (42) 0.8575	1/50 (43) 0.8838	2/50 (43) 0.7009	0/50 (43) 1.0000	5/50 (44) 0.2363
	Fibrosarcoma	0/50 (41) 0.1916	0/50 (43) NC	1/50 (43) 0.5119	1/50 (43) 0.5119	0/50 (44) NC
	Hemangioma	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	0/50 (44) NC
	Hemangiosarcoma	0/50 (41) 0.5029	1/50 (44) 0.5176	0/50 (43) NC	0/50 (43) NC	0/50 (44) NC
	Keratoacanthoma	2/50 (41) 0.5352	5/50 (43) 0.2366	2/50 (43) 0.7100	3/50 (43) 0.5229	4/50 (45) 0.3837

Organ name	Tumor name	0 mkd Vehicle C P - Trend	0.25 mkd Low (L) P - VC vs. L	0.8 mkd Mid (M) P - VC vs. M	2.5 mkd High (H) P - VC vs. H	0 mkd Water C (WC) P - VC vs. WC
	Leiomyosarcoma	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000
	Lipoma	0/50 (41) 0.7573	2/50 (43) 0.2590	0/50 (43) NC	0/50 (43) NC	2/50 (44) 0.2650
	Liposarcoma	0/50 (41) 0.5059	1/50 (43) 0.5119	0/50 (43) NC	0/50 (43) NC	0/50 (44) NC
	Osteosarcoma	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	0/50 (44) NC
	Papilloma	0/50 (41) 0.2529	0/50 (43) NC	1/50 (43) 0.5119	0/50 (43) NC	0/50 (44) NC
	Schwannoma, Malignant	1/50 (41) 0.7435	1/50 (43) 0.7648	1/50 (43) 0.7648	0/50 (43) 1.0000	2/50 (44) 0.5268
	Squamous Cell Carcinoma	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000
	Trichoepithelioma	0/50 (41) 0.1119	1/50 (43) 0.5119	0/50 (43) NC	2/50 (43) 0.2590	0/50 (44) NC
Small Intestine, Duodenum	Leiomyosarcoma	0/50 (41) NC	0/50 (43) NC	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5176
Small Intestine, Jejunum	Hemangioma	0/50 (41) 0.2529	0/50 (43) NC	0/50 (43) NC	1/50 (43) 0.5119	0/50 (44) NC
Spinal Cord	Astrocytoma, Malignant	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000
Spleen	Hemangiosarcoma	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000
Testis	Carcinoma	0/50 (41) NC	0/50 (43) NC	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5176
	Interstitial (Leydig) Cell Adenoma	0/50 (41) 0.8816	3/50 (43) 0.1295	0/50 (43) NC	0/50 (43) NC	1/50 (44) 0.5176
Thymus	Thymoma, Benign	2/48 (39) 0.6008	1/48 (41) 0.8888	3/47 (42) 0.5356	1/45 (38) 0.8751	1/49 (43) 0.8968
	Thymoma, Malignant	0/48 (39) 0.5000	1/48 (41) 0.5125	0/47 (42) NC	0/45 (38) NC	0/49 (43) NC
Urinary Bladder	Papilloma	1/50 (41) 0.7588	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (43) 1.0000	0/50 (44) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 5B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	0 mkd Vehicle C P - Trend	0.1 mkd Low (L) P - VC vs. L	0.3 mkd Mid (M) P - VC vs. M	1 mkd High (H) P - VC vs. H	0 mkd Water C (WC) P - VC vs. WC
Brain	Astrocytoma, Malignant	1/50 (44) 0.7528	0/50 (47) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000	0/50 (46) 1.0000
	Granular Cell Tumor, Benign	0/50 (43) 0.3092	1/50 (47) 0.5222	0/50 (44) NC	1/50 (43) 0.5000	1/50 (46) 0.5169
	Oligodendroglioma, Malignant	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
	Squamous Cell Carcinoma	0/50 (43) 0.2472	0/50 (47) NC	0/50 (44) NC	1/50 (44) 0.5057	0/50 (46) NC
Esophagus	Papilloma	0/50 (43) 0.2429	0/50 (47) NC	0/50 (44) NC	1/50 (43) 0.5000	0/50 (46) NC

Organ name	Tumor name	0 mkd Vehicle C P - Trend	0.1 mkd Low (L) P - VC vs. L	0.3 mkd Mid (M) P - VC vs. M	1 mkd High (H) P - VC vs. H	0 mkd Water C (WC) P - VC vs. WC
Gland, Adrenal	Cortical Adenoma	2/50 (43) 0.5041	0/50 (47) 1.0000	1/50 (44) 0.8836	1/50 (43) 0.8794	0/50 (46) 1.0000
	Cortical Carcinoma	0/50 (43) 0.3084	1/50 (48) 0.5275	0/50 (44) NC	1/50 (43) 0.5000	0/50 (46) NC
	Pheochromocytoma, Benign	0/50 (43) 0.4915	1/50 (47) 0.5222	0/50 (44) NC	0/50 (43) NC	2/50 (46) 0.2643
Gland, Mammary	Adenocarcinoma	1/49 (42) 0.4168	0/50 (47) 1.0000	0/50 (44) 1.0000	1/48 (41) 0.7470	2/49 (46) 0.5345
	Fibroadenoma	6/49 (42) 0.9921	13/50 (48) 0.1096	1/50 (45) 0.9954	2/48 (41) 0.9690	11/49 (47) 0.2061
Gland, Parathyroid	Adenoma	0/44 (38) NC	0/45 (42) NC	0/48 (42) NC	0/41 (36) NC	1/49 (45) 0.5422
Gland, Pituitary	Adenoma, Pars Distalis	17/50 (47) 0.7086	21/50 (49) 0.3226	19/50 (46) 0.3839	15/50 (44) 0.6650	25/50 (46) 0.0600
	Adenoma, Pars Intermedia	1/50 (43) 0.2279	1/50 (47) 0.7745	0/50 (44) 1.0000	2/50 (43) 0.5000	3/50 (46) 0.3342
	Carcinoma, Pars Distalis	0/50 (43) 0.0580	0/50 (47) NC	0/50 (44) NC	2/50 (43) 0.2471	1/50 (46) 0.5169
Gland, Salivary, Parotid	Squamous Cell Carcinoma	1/48 (42) 0.7572	0/48 (45) 1.0000	0/48 (43) 1.0000	0/49 (43) 1.0000	0/50 (46) 1.0000
Gland, Thyroid	C-Cell Adenoma	3/50 (43) 0.1132	2/50 (47) 0.8461	2/50 (44) 0.8270	5/50 (43) 0.3565	4/50 (46) 0.5381
	Follicular Cell Adenoma	1/50 (43) 0.7346	1/50 (47) 0.7745	2/50 (44) 0.5087	0/50 (43) 1.0000	2/50 (46) 0.5256
Heart	Schwannoma, Malignant	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
Hemolymphoretic Tissue	Histiocytic Sarcoma	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
	Leukemia, Large Granular Lymphocytic	0/50 (43) 0.2429	0/50 (47) NC	0/50 (44) NC	1/50 (43) 0.5000	0/50 (46) NC
	Lymphoma, Malignant	0/50 (43) 0.2429	0/50 (47) NC	0/50 (44) NC	1/50 (43) 0.5000	0/50 (46) NC
Kidney	Lipoma	1/50 (43) 0.7571	0/50 (47) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000	0/50 (46) 1.0000
		Liver	Hepatocellular Adenoma	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057
Lymph Node, Mesenteric	Hemangioma	1/50 (43) 0.7305	1/50 (47) 0.7745	1/50 (45) 0.7641	0/50 (43) 1.0000	0/50 (46) 1.0000
Ovary	Cystadenocarcinoma	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
	Granulosa Cell Tumor, Benign	0/50 (43) 0.2429	0/50 (47) NC	0/50 (44) NC	1/50 (43) 0.5000	1/50 (46) 0.5169
	Thecoma, Benign	1/50 (43) 0.7571	0/50 (47) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000	0/50 (46) 1.0000
Pancreas	Thecoma, Malignant	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
		Islet Cell Adenoma	0/50 (43) NC	0/49 (46) NC	0/50 (44) NC	0/50 (43) NC
Skin	Basal Cell Tumor, Malignant	0/50 (43) 0.4915	1/50 (47) 0.5222	0/50 (44) NC	0/50 (43) NC	0/50 (46) NC
	Fibroma	0/50 (43) 0.6768	2/50 (47) 0.2699	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
	Hemangiosarcoma	0/50 (43) 0.4915	1/50 (47) 0.5222	0/50 (44) NC	0/50 (43) NC	1/50 (46) 0.5169

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Organ name	Tumor name	0 mkd Vehicle C P - Trend	0.1 mkd Low (L) P - VC vs. L	0.3 mkd Mid (M) P - VC vs. M	1 mkd High (H) P - VC vs. H	0 mkd Water C (WC) P - VC vs. WC
	Keratoacanthoma	0/50 (43) 0.2429	0/50 (47) NC	0/50 (44) NC	1/50 (43) 0.5000	0/50 (46) NC
	Lipoma	0/50 (43) 0.4915	1/50 (47) 0.5222	0/50 (44) NC	0/50 (43) NC	0/50 (46) NC
	Osteosarcoma	1/50 (43) 0.7571	0/50 (47) 1.0000	0/50 (44) 1.0000	0/50 (43) 1.0000	0/50 (46) 1.0000
	Papilloma	1/50 (43) 0.8123	1/50 (47) 0.7745	0/50 (44) 1.0000	0/50 (43) 1.0000	0/50 (46) 1.0000
	Squamous Cell Carcinoma	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
	Trichoepithelioma	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
Thymus	Thymoma, Benign	4/49 (43) 0.3416	0/50 (47) 1.0000	2/48 (43) 0.8990	3/50 (43) 0.7834	0/50 (46) 1.0000
Uterus	Endometrial Adenocarcinoma	0/50 (43) 0.5104	3/50 (47) 0.1380	2/50 (44) 0.2529	1/50 (43) 0.5000	0/50 (46) NC
	Endometrial Adenoma	0/50 (43) 0.2429	0/50 (47) NC	1/50 (44) 0.5057	0/50 (43) NC	0/50 (46) NC
	Endometrial Stromal Polyp	7/50 (43) 0.4841	3/50 (47) 0.9676	4/50 (45) 0.9154	5/50 (43) 0.8244	8/50 (46) 0.5576
	Schwannoma, Malignant	0/50 (43) NC	0/50 (47) NC	0/50 (44) NC	0/50 (43) NC	2/50 (46) 0.2643

& X/ZZ (YY): X=number of tumors bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Males Mice

Organ name	Tumor name	0 mkd Control P - Trend	6 mkd Low (L) P - C vs. L	16 mkd Mid (M) P - C vs. M	50 mkd High (H) P - C vs. H	0 mkd Water (WC) P - C vs. WC	75 mg Positive (PC) P - C vs. PC
Brain	Astrocytoma, Malignant	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (22) NC	1/25 (24) 0.4898	0/15 (8) NC
Gland, Harderian	Adenoma	1/25 (25) 0.4556	1/25 (25) NC	2/25 (25) 0.5000	1/25 (22) 0.7225	0/25 (24) 1.0000	0/15 (8) 1.0000
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (22) NC	0/25 (24) NC	10/15 (13) 0.0000 **
Lung	Bronchioloalveolar Adenoma	4/25 (25) 0.9963	0/25 (25) 1.0000	0/25 (25) 1.0000	0/25 (22) 1.0000	5/25 (24) 0.4725	5/15 (9) 0.0343
Skin	Papilloma Squamous Cell Carcinoma	0/25 (25) NC 0/25 (25) NC	0/25 (25) NC 0/25 (25) NC	0/25 (25) NC 0/25 (25) NC	0/25 (22) NC 0/25 (22) NC	0/25 (24) NC 0/25 (24) NC	5/15 (9) 0.0005 ** 1/15 (8) 0.2424
Small Intestine, Ileum	Adenocarcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (22) NC	0/25 (24) NC	1/12 (6) 0.1935
Small Intestine, Jejunum	Adenoma	0/25 (25) NC	0/25 (25) NC	0/25 (25) NC	0/25 (22) NC	0/25 (24) NC	1/13 (7) 0.2188
Spleen	Hemangiosarcoma	2/25 (25) 0.8318	0/25 (25) 1.0000	1/25 (25) 0.8827	0/25 (22) 1.0000	1/25 (24) 0.8752	1/15 (9) 0.6156
Stomach	Papilloma Squamous Cell Carcinoma	0/25 (25) 0.2268 0/25 (25) NC	0/25 (25) NC 0/25 (25) NC	1/25 (25) 0.5000 0/25 (25) NC	0/25 (22) NC 0/25 (22) NC	0/25 (24) NC 0/25 (24) NC	8/15 (11) 0.0000 ** 2/15 (9) 0.0642

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Organ name	Tumor name	0 mkd Control P - Trend	6 mkd Low (L) P - C vs. L	16 mkd Mid (M) P - C vs. M	50 mkd High (H) P - C vs. H	0 mkd Water (WC) P - C vs. WC	75 mg Positive (PC) P - C vs. PC
Thymus	Thymoma, Malignant	0/25 (25) 0.2268	0/25 (25) NC	1/25 (25) 0.5000	0/25 (22) NC	0/24 (23) NC	0/15 (8) NC
Tongue	Papilloma	0/25 (25) 0.4845	1/25 (25) 0.5000	0/25 (25) NC	0/25 (22) NC	0/25 (24) NC	0/15 (8) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Table 6B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	0 mkd Control P - Trend	6 mkd Low (L) P - C vs. L	16 mkd Mid (M) P - C vs. M	50 mkd High (H) P - C vs. H	0 mkd Water (WC) P - C vs. WC	75 mg Positive (PC) P - C vs. PC
Gallbladder	Adenoma	0/24 (24) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	1/11 (7) 0.2258
Gland, Harderian	Adenoma	0/25 (25) 0.4949	1/25 (25) 0.5000	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/15 (8) NC
Hemolymphoreticular Tissue	Lymphoma, Malignant	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	11/15 (14) 0.0000 **
Large Intestine, Colon	Adenocarcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	1/14 (8) 0.2424
Lung	Bronchioloalveolar Adenoma	5/25 (25) 0.9993	0/25 (25) 1.0000	0/25 (24) 1.0000	0/25 (25) 1.0000	4/25 (25) 0.7683	4/15 (9) 0.1619
	Bronchioloalveolar Carcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	1/15 (9) 0.2647
Skin	Papilloma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	6/15 (10) 0.0001 **
	Squamous Cell Carcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	2/25 (25) 0.2449	10/15 (12) 0.0000 **
Small Intestine, Jejunum	Adenoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	2/11 (7) 0.0423 **
Spleen	Hemangiosarcoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	1/25 (25) 0.5000	1/14 (8) 0.2424
Stomach	Papilloma	1/25 (25) 0.8093	1/25 (25) NC	0/25 (24) 1.0000	0/25 (25) 1.0000	0/25 (25) 1.0000	11/14 (12) 0.0000 **
	Squamous Cell Carcinoma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	1/14 (9) 0.2647
Thymus	Thymoma, Benign	0/25 (25) 0.5052	1/23 (23) 0.4792	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	0/15 (8) NC
Vagina	Papilloma	0/25 (25) NC	0/25 (25) NC	0/25 (24) NC	0/25 (25) NC	0/25 (25) NC	2/13 (8) 0.0530

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.

Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

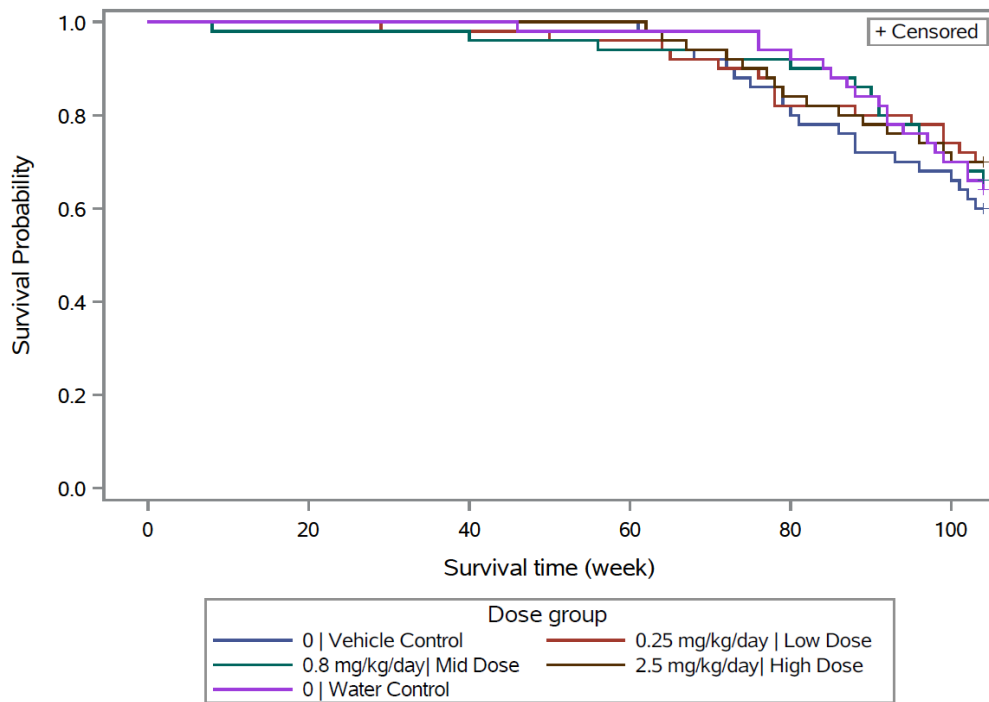


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

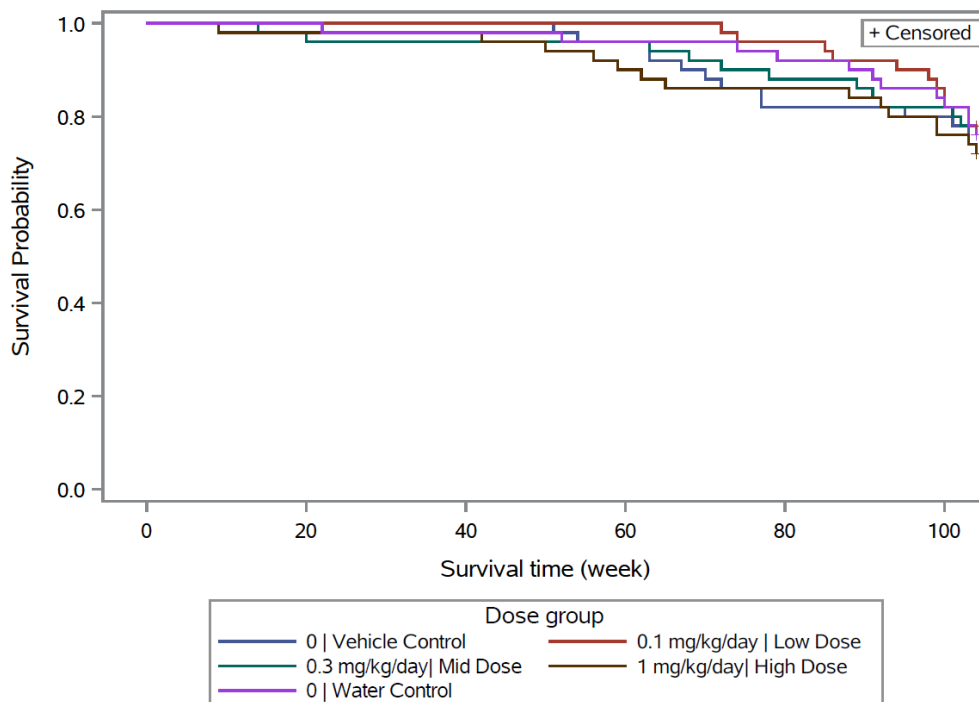


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

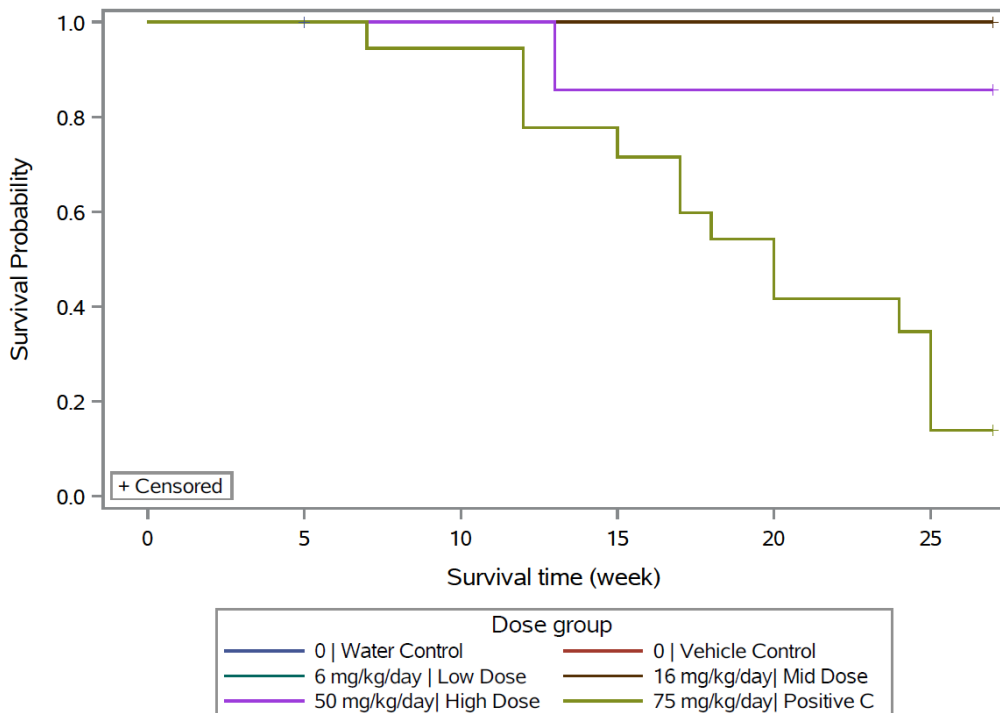
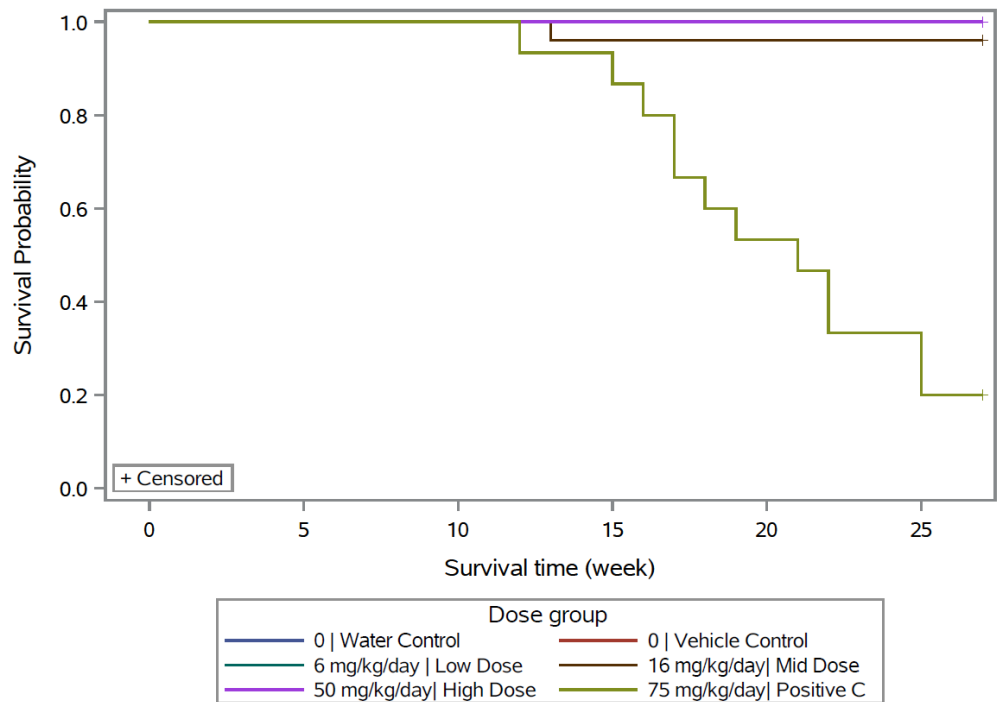


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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