Clinical Study Protocol	
Drug Substance	Selumetinib
Study Code	D1346C00011
Version	3.0
Date	30 Sep 2021

A Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Selumetinib, a Selective Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor, in Chinese Paediatric and Adult Subjects with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

Regulatory Agency Identifying Number(s):
NCT number: NCT04590235

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	30 September 2021
Amendment 1	02 March 2020
Initial creation	12 August 2019

Amendment 2 (30 September 2021)

Overall Rationale for the Amendment:

The primary rationale for this amendment is to revise the DCO timepoints and add study mitigation language which will provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to the study integrity. Additional changes incorporated are described in the below. Minor clarifications/changes are also incorporated in the body of the Clinical Study Protocol(CSP) that are not mentioned in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
1.2 Synopsis 4.4 End of study definition 9.5 Statistical analyses 9.6 Interim analyses	Revise DCO timepoints	Primary and final DCO timepoints are revised based on results from global SPRINT study, and the new primary and final DCO timepoints would provide sufficient data to evaluate safety, efficacy of selumetinib in Chinese subjects with NF1 and inoperable PN. An interim analysis is added to assess PK, safety, tolerability and efficacy data.Also, end of study time is updated according to the new final analysis DCO.	Substantial
6.1.1 Investigational products, Table 4 Dosing nomogram for the selumetinib PK study 6.6 Dose modification and discontinuation, Table 7	Revised the recommended dosage for BSA 0.55-0.69 m^2	The protocol has been aligned to the updated Global dose recommendation guidelines for Selumetinib that patients with BSA 0.55 to 0.69 m^2 should be given 20 mg in the	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Two-step Dose Modification Procedure Appendix H, Table 31 Recommended Dosage of Selumetinib for Co-administration with Strong or Moderate CYP3A4 or CYP2C19 Inhibitors		morning and 10 mg in the evening. The recommended dose reductions for this BSA bracket have also been updated in line with the Global dose reduction recommendation guidelines for Selumetinib.	
4.1.1 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis Appendix J	Added guidance on study continuity in event of public health or civic crisis	This section details the measures that may be implemented if a participant is not able to visit a study site whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.	Substantial
8.3.11 Adverse events of special interest	Update Table 11 to follow latest project specific safety requirements from global safety for reorganizing AESI	Follow global streamlined AESI list which was organized based on the understanding of the safety profile in adult patients with advanced cancer and paediatric patients with NF1 related symptomatic inoperable PN combined with the safety knowledge gained from global submission activities, and to focus on significant medical/clinical concepts.	Substantial
Table 1: Scheduled of assessments	Remove the visit window of C1D8	Subjects need to hospitalized for intensive PK collection. Removal of visit window will minimize the operation burden and ensure the PK collection smoothly.	Non-Substantial
1.2 Synopsis 2.1 Study rationale	Revise wordings for the study objectives for	Wordings describing study objectives are revised to	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	paediatric and adult cohorts	keep consistent with Table. 2 study objectives.	
Appendix H Table 33	The drug-drug interactions guidance are updated to recommended dose reductions if a strong or moderate CYP3A4 or CYP2C19 inhibitor must be co-administered with selumetinib. Remove CYP2C19 column in Table 33	The protocol has been aligned to the updated Global recommendation guidelines for Selumetinib. CYP2C19 has a smaller contribution to selumetinib metabolism, compared to CYP3A4, and no PKPD relationship has been observed for efficacy therefore CYP2C19 inducers are permitted	Non-substantial

Amendment 1 (2 March 2020)

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Table 1; 8.5 Pharmacokinetics: Table 11 & 12	Updated PK sample collection time point	Based on the half-life of selumetinib, adjusted PK timepoint	Non-substantial
1.2 Synopsis & Table 2 - Secondary objective; 9.4.3.1.1 Objective response rate	Clarify confirmed response definition	Clarify how a PR is deemed to be 'confirmed' as per approach in SPRINT Phase II Stratum 1.	Non-substantial
1.2 Synopsis: Treatments and treatments duration	Add reference for BSA calculation formula for paediatric subjects	Based on China local guideline as reference	Non-substantial
1.2 Synopsis: Treatments and treatments duration; 4.4 End of study definition; 8.5 Pharmacokinetics;	Interim analysis wording was removed	Preliminary PK analysis wouldn't trigger DBL and DCO, thus it's inappropriate to call it interim. Thus, the wording of "interim" is removed.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
9.5 Statistical analyses; 9.6 Interim analyses			
1.2 Synopsis: Treatments and treatments duration; Figure 1. Study Design; 4.4 End of study definition; 9.5 Statistical analyses	Revise wording to specify the primary and final DCOs	Clarification of 2 DCOs	Non-substantial
2.2 Background; 2.3.1 Overall benefit/risk assessment; 4.2 Scientific rationale for study design	Update Clinical data of SPRINT Phase I and Phase II	Based on SPINT study CSR of Phase I and Phase II stratum I	Non-substantial
4.1 overall design; 5.1 inclusion criteria 6	Add definition of PN subtypes and clarify that solitary nodular PN cannot be selected as the target or non-target PN; Clarify that the target PN must be classified as either typical or nodular (ie must not be solitary nodular) Remove lesion measurability and suitability confirmation prior to enrolment	The definition is consistent with SPRINT and confirmed by Dr. Eva Dombi Clarify that a solitary nodular PN cannot be selected as the target or non-target PN as solitary nodular PN may have different biology and respond differently to treatment. MRI acquisition training will be provided to sites to mitigate the risk of enrolling subjects where baseline MRI is low quality/ target PN not measurable	Non-substantial
4.3 Justification for dose	Updated Clinical data of SPRINT Phase I and Phase II Stratum I	Based on SPRINT study CSR of Phase I and Phase II stratum I	Non-substantial
6.1.1 Investigational products	Update instruction for next dosing if scheduled dose missed	Based on PK characteristics	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
6.6 Dose modification and discontinuation	Clarified Dose modification plan	Based on Toxicity Management Guideline	Non-substantial
7.1 Discontinuation of study treatment	Patients who achieved PR and then meet the criteria of PD to be permitted to remain on study treatment as long as their PN remain less than 20% above baseline and receiving clinical benefit	Updated to be consistent with latest SPRINT CSP.	Non-substantial
7.1.3 Procedures for discontinuation of study treatment	Added the wording on tumour assessment follow up schedule	To assess the response of selumetinib on tumour, continued tumour assessment is required in study subjects who discontinued study treatment due to reason other than disease progression	Non-substantial
8.1.1 Tumour response	Provided details for image collection and review process Redefinition on the non-target lesion Clarification on the definition of unequivocal progression Clarification on the confirmed partial response	Clarification of image collection process REiNS guidance doesn't specify the number of non-target lesions to be followed or the definition of 'unequivocal progression' of a non-target lesion. Based on learnings from SPRINT, one clinically relevant non-target as well as the target PN is sufficient to represent disease burden In SPRINT, 'unequivocal progression' of non-target PN required the investigator to assess the lesion as clinically relevant as well as volumetric progression. Therefore, definition of 'unequivocal progression' was updated to reflect practice in SPRINT. Clarify how a PR is deemed to be 'confirmed' as per approach in SPRINT Phase II Stratum 1.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
8.1.3.1.1 FLACC pain scale (3 years)	FLACC pain scale training provided to paediatric subjects' parents	Clarification of operational process of FLACC pain scale	Non-substantial
8.1.3.1.2 Faces pain scale - revised (4 to 17 years)	Updated instructions on how to manage subjects who are unable to read	Provide guidance to handle the scenario when subject have difficulties reading the Faces pain scale.	Non-substantial
8.1.3.1.3 NRS-11 (adult cohort only)	Updated the characteristic and number of selected pain	Based on the data of SPRINT phase II stratum I study	Non-substantial
8.1.3.1.5 Pain medication survey (all subjects); Table 8; Appendix I – Pain Medication survey	Updated pain medication survey will be collected on paper	Adoption of paper version due to the limitation of free text in electronic COA version	Non-substantial
8.1.3.6 administration of COAs	Added a section on administration of COAs	Provide guidance on how to administer of COAs	Non-substantial
Appendix E Guidance for management of specific adverse events	Added guidance for management of paronychia. Update existing guidance to make it clearer and easy-execution for both adult and paediatric patients.	Updated or New information from global updated Toxicity Management Guidelines (TMG) documents.	Non-substantial
Appendix G Performance status scales	Updated the Performance status scales	Updated scale	Non-substantial
Appendix H	Remove CYP1A2 inhibitors/inducers, and related concomitant medications	Based on new safety information	Non-substantial
Appendix I Clinical outcome assessments	Updated questionnaires with formal versions and replaced watermarked versions	Obtained clear versions of questionnaires from licence holders	Non-substantial
Whole CSP, in addition to above key changes	1. Few sections updated for maintaining	1. Changes are aligned with wording elsewhere in the CSP section	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	consistency across document 2. Minor corrections /changes made for typos.	2. Wording revise to make statement clearer 3. Few sections are aligned with new CSP template	

This clinical study protocol (CSP) has been subject to a peer review according to AstraZeneca Standard procedures. The CSP is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

Protocol Number: D1346C00011

Amendment Number: amendment 1

Study Intervention: selumetinib

Study Phase: Phase I

Medical Monitor Name and Contact Information will be provided separately

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1. PROTOCOL SUMMARY

1.1 Schedule of activities

Table 1 Schedule of assessments

Visits[a] / Activities/ Assessments	Screening[b]	C0		C1			C2	C3	C4	C5 to C12	C13 to C24	C>24[c]	EoT[d]	30-day Safety Follow-up (Adult and Paediatric)[e]	Long-term Post-treatment safety Follow-up (Paediatric Only)[f]	Details in section
Day of each cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**NA**	**NA**	**NA**	
Study day	**-28 to -1**	**1**	**2**	**3**	**10**	**30**	**58**	**86**	**114**	**142 to 338**	**366 to 674**	**>674**	**NA**	**EoT + 30 days**	**Up to EoT + 1 year**	
Visit window (days)		**0**	**0**	**0**	**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**	**+7**	**±7**	
Informed consent	X															Section 5.1
Inclusion/exclusion criteria	X															Sections 5.1 and 5.2
Hospitalisation		X[g]	X[g]		X[g]											Sections 4.1 and 8.5
Routine clinical procedures																
Demography	X															Section 5.1
Medical history	X															Sections 5.1 and 5.2
Hepatitis serology, HBV PCR[h], HCV PCR[i]	X															Section 5.2
Concomitant medications/treatments	←														→	Section 6.5
Routine safety measurements																

Visits[a] / Activities/ Assessments	Screening[b]	C0		C1			C2	C3	C4	C5 to C12	C13 to C24	C>24[c]	EoT[d]	30-day Safety Follow-up (Adult and Paediatric)[e]	Long-term Post-treatment safety Follow-up (Paediatric Only)[f]	Details in section
Day of each cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**NA**	**NA**	**NA**	
Study day	**-28 to -1**	**1**	**2**	**3**	**10**	**30**	**58**	**86**	**114**	**142 to 338**	**366 to 674**	**>674**	**NA**	**EoT + 30 days**	**Up to EoT + 1 year**	
Visit window (days)		**0**	**0**	**0**	**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**	**+7**	**±7**	
Clinical chemistry (fasting)[j]	X				X	X	X	X	X	X	X	X	X	X		Section 8.2.1
Haematology[j]	X				X	X	X	X	X	X	X	X	X	X		Section 8.2.1
Urinalysis[j]	X				X	X	X	X	X	X	X	X	X	X		Section 8.2.1
Pregnancy test[k]	X	X				X	X	X	X	X	X	X	X			Section 8.2.1.1
Physical examination[j,l]	X	X		X	X	X	X	X	X	X	X	X	X	X		Section 8.2.2
Vital signs[j,m]	X	X		X	X	X	X	X	X	X	X	X	X	X		Section 8.2.3
Height and weight[j,n]	X	X				X	X	X	X	X	X	X	X	X	X	Section 8.2.4
ECG[j,o]	X					X	X	X	X	X	X	X	X	X		Section 8.2.5
Echocardiogram[j,p]	X					X	X	X	X	X	X	X	X	X		Section 8.2.6
Ophthalmologic examination[j,q]	X					X	X	X	X	X	X	X	X	X		Section 8.2.7
X-Ray (hand and wrist; paediatric cohort)[r]	X															Section 8.2.9
Tanner stages (paediatric cohort) and performance status[j]	X					X	X	X	X	X	X	X	X	X	X	Sections 8.2.8 and 8.2.10
AEs[s]	←														→	Section 8.3

Visits[a] / Activities/ Assessments	Screening[b]	C0		C1			C2	C3	C4	C5 to C12	C13 to C24	C>24[c]	EoT[d]	30-day Safety Follow-up (Adult and Paediatric)[e]	Long-term Post-treatment safety Follow-up (Paediatric Only)[f]	Details in section
Day of each cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**NA**	**NA**	**NA**	
Study day	**-28 to -1**	**1**	**2**	**3**	**10**	**30**	**58**	**86**	**114**	**142 to 338**	**366 to 674**	**>674**	**NA**	**EoT + 30 days**	**Up to EoT + 1 year**	
Visit window (days)		**0**	**0**	**0**	**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**	**+7**	**±7**	
Efficacy measurements																
Tumour assessments[t]	X								X	X	X	X	X			Section 8.1.1
Disfigurement[u]	X									X	X					Section 8.1.2
Clinical outcome assessments																
FLACC pain scale (3 years only)[v]		X				X	X	X	X	X	X	X	X			Section 8.1.3.1.1
Faces pain scale - revised (4 to 17 years only)[v]		X				X	X	X	X	X	X	X	X			Section 8.1.3.1.2
NRS-11 (adult cohort)[v]		X				X	X	X	X	X	X	X	X			Section 8.1.3.1.3
PII[v,w]		X				X	X	X	X	X	X	X	X			Section 8.1.3.1.4
Pain medication survey[v]		X				X	X	X	X	X	X	X	X			Section 8.1.3.1.5
PedsQL (paediatric cohort)[v,x]		X				X	X	X	X	X	X	X	X			Section 8.1.3.2.1
EORTC QLQ-C30 (adult cohort)[v]		X				X	X	X	X	X	X	X	X			Section 8.1.3.2.2

Visits[a] / Activities/ Assessments	Screening[b]	C0		C1			C2	C3	C4	C5 to C12	C13 to C24	C>24[c]	EoT[d]	30-day Safety Follow-up (Adult and Paediatric)[e]	Long-term Post-treatment safety Follow-up (Paediatric Only)[f]	Details in section
Day of each cycle	**-28 to -1**	**1**	**2**	**1**	**8**	**28**	**28**	**28**	**28**	**28**	**28**	**28**	**NA**	**NA**	**NA**	
Study day	**-28 to -1**	**1**	**2**	**3**	**10**	**30**	**58**	**86**	**114**	**142 to 338**	**366 to 674**	**>674**	**NA**	**EoT + 30 days**	**Up to EoT + 1 year**	
Visit window (days)		**0**	**0**	**0**	**0**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**	**+7**	**±7**	
PlexiQoL (adult cohort)[v]		X				X	X	X	X	X	X	X	X			Section 8.1.3.2.2
Physical functioning (PROMIS)[v,y]		X				X	X	X	X	X	X	X	X			Section 8.1.3.3
PGIS[v,z]		X				X	X	X	X	X	X	X	X			Section 8.1.3.4
PGIC[v,z]						X	X	X	X	X	X	X	X			Section 8.1.3.5
Pharmacokinetic measurements																
PK blood samples[g]		X	X		X											Section 8.5
Study treatment administration																
Dispense/return of selumetinib[aa]		X		X		X	X	X	X	X	X	X				Section 6
Study treatment compliance[bb]		X		X		X	X	X	X	X	X	X				Section 6.4

AE=adverse event; anti-HBc=hepatitis B core antibody; BP=blood pressure; C=cycle; DNA=deoxyribonucleic acid; ECG=electrocardiogram; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EoT=end of treatment; FLACC=Face, Legs, Activity, Cry, Consolability; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; NA=not applicable; NRS=Numeric Rating Scale; PCR=polymerase chain reaction; PedsQL=Paediatric Quality of Life Inventory; PGIC=patient's global impression of change; PGIS=patient's global impression of severity; PII=Pain Interference Index; PK=pharmacokinetics; PlexiQoL=plexiform neurofibromas quality of life scale; PROMIS=Patient-Reported Outcomes Measurement Information System; RNA=ribonucleic acid.

[a] Assessments will be performed at the end of each cycle. Selumetinib will be dispensed after all assessments have been performed and the next cycle will begin at that point.

[b] Screening tests should be performed within 28 days before the first administration of study treatment, unless otherwise indicated.
[c] Treatment with selumetinib may be continued until disease progression or unacceptable drug-related toxicity, whichever occurs first.
[d] The EoT visit will be performed for subjects who permanently discontinue study treatment for any reason (except for death, lost to follow-up or withdrawal of consent).
[e] The 30-day safety follow-up assessments will be conducted at 30 days post-last dose/EoT for both paediatric and adult cohorts.
[f] Long-term post-treatment safety follow-up assessments will be conducted for 1 year (at 6 and 12 months post-treatment) for paediatric subjects only.
[g] Subjects need to be hospitalised for intensive PK sampling during the single dose period (from Cycle 0 Day -1 to Cycle 0 Day 2) and on Cycle 1 Day 8. During Cycle 0, PK samples will be collected pre-dose, 30 minutes, and 1, 1.5, 3, 6, 8, 12, 24 and 30 hours post-dose. At Cycle 1 Day 8, PK sample time points will be collected pre-dose, 30 minutes, and 1.5, 3, 6, and 12 hours post-dose.
[h] Subjects who are anti-HBc positive and who are HBsAg negative will need to have a negative HBV DNA PCR result before enrolment.
[i] Subjects who are hepatitis C antibody positive will need to have a negative HCV RNA PCR result before enrolment.
[j] Assessments will be performed at screening and at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, as long as the subject remains on study treatment. Assessments may also be performed at other visits during Cycles 0 and 1, as detailed. Screening assessments are suggested to be performed as close to Cycle 0 Day 1 and within 14 days.
[k] Pregnancy testing will be performed at screening, Cycle 0 Day 1 and at the end of each cycle in women of childbearing potential only (see Section 5.1) and more frequently, if clinically indicated. A urine or serum pregnancy test is acceptable. Screening assessments are suggested to be performed as close to Cycle 0 Day 1 and within 14 days.
[l] The complete physical examination includes an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.
[m] Axillary temperature, pulse rate, oxygen saturation by pulse oximetry, respiratory rate, and BP will be assessed. Assessments of BP and pulse rate should be assessed in a sitting position and preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g. television, cell phones). Manual techniques will be used only if automated devices are not available.
[n] Height and weight measurements will be performed in light clothing and with shoes off.
[o] Subjects should be supine and at rest 5 minutes prior to recording the ECG.
[p] The subject should be examined using the same machine and operator throughout the study wherever possible.
[q] Ophthalmologic assessments may be performed more often, if clinically indicated.
[r] An x-ray will be performed at screening and at other visits/cycles, if clinically indicated.
[s] AEs will be collected from the time of signing the informed consent form, throughout the treatment period, and including the follow-up period.
[t] Tumour assessments will be performed at screening and every 4 cycles (16±1 weeks) up to the end of Cycle 24 (i.e. at the end of Cycles 4, 8, 12, 16, 20, and 24). From the end of Cycle 24, tumour assessments will be performed every 6 cycles (24±1 weeks) as long as the subject remains on study treatment or until disease progression. Subjects who discontinue study treatment due to reasons other than disease progression will continue to undergo tumour assessments for approximately 1 year, if clinically applicable, and the assessment schedule should continue per the regular tumour assessment interval.
[u] Disfigurement assessments will be performed at screening and at the end of Cycles 8, 16 and 24 as long as the subject remains on study treatment.
[v] Baseline clinical outcome assessments should be performed prior to and as close to the first dose of selumetinib as possible (PGIC should not have any baseline assessments). Post-baseline assessments should be performed at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, as long as the subject remains on study treatment. In the pediatric cohort, the pain medication survey will be completed on paper by the parent. In the adult cohort, the pain medication survey will be completed on paper by the patients. Other assessments will be performed electronically using on-site tablets.

[w] Adults and children from 8 to 17 years of age will complete self-reported PII; parents/legal guardian of children from 5 to 17 years of age will complete the parent proxy PII.

[x] Subject-reported versions are for subjects aged 5 to 7 years, 8 to 12 years, and 13 to 17 years. In addition, the corresponding parent-reported versions will also be included. For subjects 3 to 4 years of age, only the parent-reported version will be included.

[y] Self-reported short forms will be administered to children from 8 to 17 years of age and parallel parent proxy forms to children aged from 5 to 17 years. In the adult cohort, a newly developed PROMIS short form physical functioning scale will be used.

[z] Will be parent-reported for children aged up to 17 years and self-reported for children aged 8 to 17 years and adults.

[aa] Following screening, all eligible subjects will first receive a single oral dose of selumetinib 25 mg/m^2 (Cycle 0). After a period of 2 days, oral selumetinib 25 mg/m^2 twice daily (approximately every 12 hours) will be administered continuously for 28-day cycles (starting at Cycle 1) with no rest periods between cycles. Selumetinib will be dispensed after all assessments have been performed and the next 28-day cycle will begin at that point. Subjects will therefore be required to attend the site monthly to receive selumetinib. Selumetinib must be taken on an empty stomach (no food or drink other than water for 2 hours before and 1 hour after dosing) with water only.

[bb] Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

1.2 Synopsis

National coordinating investigator

[redacted] Qingfeng Li, [redacted] Shanghai Ninth People's Hospital affiliated to Shanghai JiaoTong University, School of Medicine, 639 Zhizaoju Road, Shanghai, China

Protocol Title: A Phase 1 Open Label Study to Assess the Safety, Tolerability, Pharmacokinetics and Clinical Efficacy of Selumetinib, a Selective Mitogen Activated Protein Kinase Kinase (MEK) 1 Inhibitor, in Chinese Paediatric and Adult Subjects with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN)

Rationale:

This is the first study designed to evaluate the safety, tolerability, pharmacokinetics (PK) and efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN. The evaluations of pediatric cohort and adult cohort will be conducted separately. The paediatric cohort is designed to meet a Chinese regulatory requirement to provide safety, tolerability and PK data of selumetinib in the Chinese paediatric population to support selumetinib registration in China. The adult cohort is designed to evaluatethe safety, tolerability, PK and efficacy of selumetinib in adult subjects with NF1 and inoperable PN. The study is supported by available clinical data from the ongoing SPRINT study in paediatric subjects with NF1 and inoperable PN (NCT01362803), an ongoing National Cancer Institute sponsored study in adults with NF1 and inoperable PN (NCT02407405), and clinical data of selumetinib in different tumour types.

Objectives and endpoints

Primary objectives:	Endpoints:

To assess the safety and tolerability of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN	**Paediatric and adult cohorts:** Safety and tolerability will be evaluated in terms of adverse events (AEs), clinical safety laboratory assessments, physical examination, vital signs, height/weight, electrocardiogram (ECG), echocardiogram, ophthalmologic assessment and performance status. **Paediatric only:** Safety and tolerability will also be evaluated in terms of bone growth and Tanner stages. **Assessments related to AEs will include:** • Occurrence/frequency. • Relationship to investigational product (IP) as assessed by the investigator. • Common Terminology Criteria for Adverse Events (CTCAE) grade. • Seriousness. • Death. • AEs leading to discontinuation of IP. • AEs of special interest.
To characterise the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Chinese paediatric and adult subjects with NF1 and inoperable PN	PK parameters for selumetinib and N-desmethyl selumetinib will be derived following single dose and multiple doses. These may include, but are not limited to: **After a single dose:** • Area under the concentration-time curve from zero to infinity (AUC). • Area under the concentration-time curve from zero to 12 hours (AUC_{0-12}). • Area under the concentration-time curve from zero to the last measurable concentration (AUC_{0-t}). • Maximum plasma concentration (C_{max}). • Time to maximum plasma concentration (t_{max}). • Terminal half-life ($t_{1/2}$). **After multiple doses:** • Area under the concentration-time curve from zero to 12 hours at steady-state ($AUC_{0-12,ss}$). • Maximum steady-state plasma concentration ($C_{max,ss}$). • Accumulation ratio (Rac).
Secondary objectives:	**Endpoints:**

To evaluate the clinical efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN on objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), time to progression (TTP), and time to response (TTR)	ORR is defined as the proportion of subjects who have a complete response. or confirmed partial response (defined as a target PN volume decrease ≥20% compared to baseline, confirmed by a consecutive scan within 3 to 6 months after first response, as determined by the investigator and independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression or death in the absence of disease progression, as determined by the investigator and independent central review per REiNS criteria. PFS is defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review, or death due to any cause. TTP is defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review. TTR is defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed), as determined by the investigator and independent central review per REiNS criteria.
To evaluate the effect of selumetinib on pain in Chinese paediatric and adult subjects with NF1 and inoperable PN	• Face, Legs, Activity, Cry, Consolability (FLACC) scale (3 years of age). • Faces pain scale - revised (4 to 17 years of age). • Numeric Rating Scale (NRS-11; adult cohort). • Pain Interference Index (PII; adult cohort; self- and parent re-ported in the paediatric cohort). • Pain Medication Survey (self-reported in the adult cohort; parent-reported in the paediatric cohort).
To determine the effect of selumetinib on health-related quality of life	• Paediatric Quality of Life Inventory (PedsQL; paediatric cohort – self- and parent-reported). • European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; adult cohort) and PN quality of life scale (PlexiQoL; adult cohort).
To determine the effect of selumetinib on physical functioning	• Patient-Reported Outcomes Measurement Information System (PROMIS; upper extremity; self- and parent reported- in the paediatric cohort). • PROMIS (mobility; self- and parent reported- in the paediatric cohort). • PROMIS Physical Function - Short Form 8c 7-day (adult cohort).
Exploratory objectives:	**Endpoints:**
To evaluate patient's global impression of severity (PGIS) of symptoms	• PGIS (adult cohort; self- and parent-reported in the paediatric cohort).

To evaluate patient's global impression of change (PGIC) in symptoms	• PGIC (adult cohort; self- and parent-reported in the paediatric cohort).
To determine the effect of selumetinib on disfigurement	• Photographic evaluation.
Safety objective: contained within the primary objectives.	

Overall design:

This is an open label Phase 1 study with 2 independent cohorts to assess the safety, tolerability, PK and clinical efficacy of selumetinib in Chinese paediatric and adult subjects with a clinical diagnosis of NF1 per National Institutes of Health (NIH) guidelines (NIH Consensus Development Conference Statement 1988) and inoperable measurable PNs that require treatment due to symptoms or with the potential to develop significant clinical complications. Approximately 16 paediatric and 16 adult subjects with NF1 and inoperable PN will be enrolled in the study in China. The assignment to treatment and evaluation of efficacy and safety will be performed independently for each cohort. The Safety Review Committee (SRC) will evaluate preliminary tolerability, safety and available PK data after the first 6 subjects in both cohorts have been treated for approximately 3 cycles. Additional enrolment will be initiated per SRC recommendation. Detailed information will be provided in the SRC charter.

Study period:

Estimated date of first subject enrolled: Quarter (Q)4 2020

Estimated date of last subject completed: Q4 2023

Number of subjects:

Approximately 16 paediatric and 16 adult subjects with a clinical diagnosis of NF1 and inoperable PN will be enrolled in the study to obtain adequate PK and safety data. Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be enrolled in the study.

Treatments and treatment duration:

Following the screening period (Day -28 to Day -1), all eligible subjects will first receive a single oral dose of selumetinib 25 mg/m^2 (Cycle 0). After a period of 2 days, oral selumetinib 25 mg/m^2 twice daily (approximately every 12 hours) will be administered continuously for 28-day cycles (starting at Cycle 1) with no rest periods between cycles. Subjects should be instructed to take the dose of selumetinib on an empty stomach (no food or drink other than water for 2 hours before and 1 hour after dosing) with water only. The capsules cannot be crushed and must be swallowed whole.

Dosing will be performed based on body surface area (BSA) calculated by the equation below, and doses will be rounded to the nearest 5 to 10 mg using a dosing nomogram. BSA should be calculated at screening and every tumour assessment visit. The dose of selumetinib will be capped at 50 mg when BSA is ≥1.9 m^2. At follow-up evaluations during tumour assessment visits, the dose of selumetinib will be adjusted for changes in BSA according to the dosing nomogram.

*For paediatric subjects with a body weight ≤30 kg:

BSA (m^2) = body weight (kg) × 0.035 + 0.1

*For paediatric subjects with a body weight ≥30 kg:

BSA (m^2) = 1.15 + (body weight [kg] - 30) × 0.02

For all adult subjects:

BSA (m^2) = 0.0061 × height (cm) + 0.0128 × body weight (kg) - 0.01529

*For paediatric subjects the BSA calculation was refer from China National Formulary (Chemicals and Biological Products for Children) 2013 version.

Subjects will continue to receive selumetinib until disease progression or unacceptable drug-related toxicity, whichever occurs first. All subjects will be evaluated for safety and efficacy at a regular basis, as defined in Table 1.

The 30-day safety follow-up visits will be conducted at 30 days post-last dose/end of treatment for both paediatric and adult cohorts. Long-term post-treatment safety follow-up assessments will be conducted for 1 year (at 6- and 12-months post-treatment) for paediatric subjects only.

For subjects who discontinue study treatment due to reasons other than disease progression, tumour assessments will continue for approximately 1 year, if clinically applicable, and the assessment schedule should continue per the regular tumour assessment interval.

To minimise bias, tumour assessments, measured by 3D volumetric magnetic resonance imaging will be determined by independent central review according to REiNS criteria (PR defined as a PN volume decrease of ≥20% compared to baseline).

Same DCOs would be applied for both analysis of pediatric cohort and adult cohort. Primary DCO in this study will take place when the last subject dosed has had the chance to complete their visit at the end of cycle 10. Final DCO will occur when the last subject dosed has had the

chance to complete their visit at the end of cycle 24. In addition, an interim analysis will be conducted when last subject dosed has had the chance to complete their visit at the end of cycle 4 to assess PK, safety, tolerability and efficacy in Chinese subjects with NF1 and inoperable PN.

AEs may result in selumetinib dose modification, including treatment interruption, dose reduction and permanent discontinuation.

Statistical methods

The primary objectives are to evaluate the safety, tolerability and PK of selumetinib. Approximately 16 paediatric and 16 adult subjects with NF1 and inoperable PN will be enrolled in the study to obtain adequate PK and safety data. Per the Chinese Phase 1 PK guideline, at least 8 to 12 subjects per cohort are required. To allow for dropouts and nonevaluable cases, 16 subjects in each cohort will be enrolled. There must be a minimum of 6 subjects each in the 3 to 11 and 12 to 17 year age groups for the paediatric cohort.

The PK analysis set will include all subjects who received at least 1 dose of selumetinib and have at least 1 post-dose evaluable concentration-time data point. PK data will be listed and summarised as appropriate by cohort. Plasma concentrations will be summarised by cohort, analyte, dose level (if applicable), and nominal sample time. The derived PK parameters (including but not limited to AUC, AUC_{0-12}, AUC_{0-t}, C_{max}, t_{max}, and $t_{1/2}$ after a single dose, and $AUC_{0-12,ss}$, $C_{max,ss}$, and Rac after multiple doses) will be summarised by cohort, analyte, and dose level (if applicable). Individual and geometric mean concentrations will be presented graphically by cohort and analyte as appropriate (i.e. for selumetinib and its metabolite, Ndesmethyl selumetinib).

The safety analysis set will include all subjects who received at least one dose of selumetinib, and will be used for safety analyses. Safety data will be presented using descriptive statistics and by cohort unless otherwise specified. All AEs, in terms of Medical Dictionary for Regulatory Activities system organ class, preferred term and CTCAE grade, will be listed. Treatment-emergent AEs (AEs with onset date on or after the first dose date or worsening of preexisting events on or after the first dose date, both within 30 days after the last dose of IP) will be summarised descriptively. Clinical safety laboratory data (haematology, clinical chemistry and quantitative urinalysis) will be summarised using descriptive statistics over time in terms of absolute values and changes from baseline. Shift tables showing CTCAE grade changes from baseline on treatment will be produced by laboratory parameter for haematology and clinical chemistry.

All vital signs, height, weight and BSA will be summarised using descriptive statistics over time in terms of absolute values and changes from baseline. Other safety assessments (pregnancy test, physical examination, ECG, echocardiogram, ophthalmologic examination,

performance status, bone growth monitoring and Tanner staging) will be listed and summarised where appropriate. Box plots of laboratory and vital signs data may be provided if needed.

Efficacy analyses will be based on the safety analysis set unless otherwise noted. ORR with corresponding 95% 2-sided exact confidence intervals based on the Clopper-Pearson method (Clopper and Pearson 1934) will be presented. The other secondary efficacy endpoints will be summarised as appropriate.

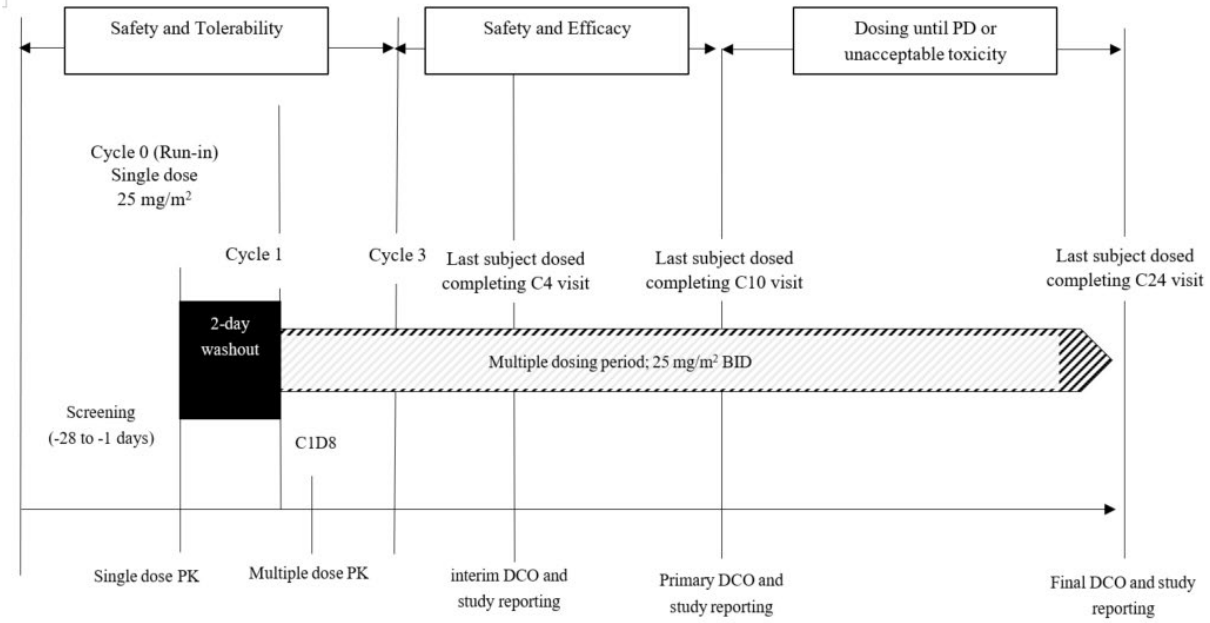
All functional and clinical outcome assessment analyses will be performed on the safety analysis set unless otherwise noted. The analysis of the clinical outcome assessments and functional outcomes will be based on descriptive statistics.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design

BID=twice daily; Cn



Dn=Cycle n Day n; DCO=data cut-off; PD=progressive disease; PK=pharmacokinetics; SRC=Safety Review Committee.
Cohort 1: Paediatric cohort = 16 subjects.
Cohort 2: Adult cohort = 16 subjects.
The SRC will evaluate preliminary tolerability and safety data, as well as PK data (if available) after the first 6 subjects in both cohorts have been treated for approximately 3 cycles. Additional enrolment will be initiated per SRC recommendation.
Long-term post-treatment safety follow-up assessments will be conducted for 1 year (at 6- and 12-months post-treatment) for paediatric subjects only.

2. INTRODUCTION

2.1 Study rationale

This is the first study designed to evaluate the safety, tolerability, pharmacokinetics (PK) and efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN. The evaluations of pediatric cohort and adult cohort will be conducted separately. The paediatric cohort is designed to meet a Chinese regulatory requirement to provide safety, tolerability and PK data of selumetinib in the Chinese paediatric population to support selumetinib registration in China. The adult cohort is designed to evaluate the safety, tolerability, PK and efficacy of selumetinib in adult subjects with NF1 and inoperable PN. The study is supported by available clinical data from the ongoing SPRINT study in paediatric subjects with NF1 and inoperable PN (NCT01362803), an ongoing National Cancer Institute

(NCI) -sponsored study in adults with NF1 and inoperable PN (NCT02407405), and clinical data of selumetinib in different tumour types.

2.2 Background

NF1 is an autosomal dominant disorder with a prevalence of approximately 1 in 2700 (Gutmann et al 2013a; Monroe et al 2017) and an incidence of 1 in 3500 (Ferner et al 2007) in the United States (US). It is characterised by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations. NF1 symptoms generally manifest very early in life and the subsequent increase in morbidity can be severe.

NF1 results from a germline mutation in the NF1 tumour-suppressor gene (Pemov et al 2017). NF1 is located on chromosome 17q11.2 and encodes a 220 kDa cytoplasmic protein called neurofibromin (Hirbe and Gutmann 2014). This protein functions, in part, as a negative regulator of the Ras proto-oncogene, which is a key signalling molecule in the control of cell growth (Gutmann et al 2012). Affected individuals start life with one mutated (nonfunctional) copy and one functional copy of NF1 in every cell in their body. Although many of the clinical features of this syndrome are apparent from birth, complete loss of gene function is needed for tumour formation through acquisition of a somatic NF1 mutation in selected cells (Ruggieri and Packer 2001; Gutmann et al 2013b).

PNs develop in 20% to 50% of individuals with NF1. Most NF1-related PNs are congenital or occur very early in life and are characterised by slow growth, complex shape, and sometimes very large size (up to 20% of body weight) (Korf 1999; Mautner et al 2008). These tumours can cause severe morbidity such as pain, neurological dysfunction, and disfigurement and also have the potential to transform to malignant peripheral nerve sheath tumours (MPNSTs) (Nguyen et al 2011; Prada et al 2012). The lifetime incidence of MPNSTs in NF1 is 15.8%, and many MPNSTs arise in pre-existing PNs (Uusitalo et al 2016).

PNs in NF1 patients are histologically benign Schwann-cell tumours (Wu et al 2005; Rutkowski et al 2000) that, depending on the location and the growth rate, bear all the characteristics typical of cancers. There is a high unmet medical need for patients with NF1 and inoperable PN as there are no approved medical treatments to cure, prevent or reverse the disease. A number of medical treatments have undergone evaluation in early clinical studies for subjects with NF1-related PNs, but these studies have reported only moderate to no clinical activity, and no systemic therapy has been shown to induce consistent and durable tumour shrinkage. Since these relentlessly growing tumours induce co-morbidities that impact children from early childhood through adolescence and their entire lifespan, patients with inoperable and progressive PNs suffer from a significant unmet medical need.

There are no epidemiological data to estimate the actual incidence or prevalence of NF1 in China. It is believed that the clinical picture of NF1, including NF1 and inoperable PN, in China is in line with that observed globally. Debulking surgery, which is complex and difficult, is the only available treatment for suitable patients with PN, who are always in a distressing condition both physically and mentally. Only a few patients may eventually receive surgery. There is therefore a significant unmet medical need for patients with NF1 and inoperable PN in China.

In the clinical setting, treatment with selumetinib in the Phase 1 SPRINT study resulted in confirmed partial responses (PRs; tumour volume decreases from baseline of ≥20%) in 16/24 (66.7%) children. The response rate was confirmed in SPRINT Phase II Stratum 1. The overall response rate by NCI POB central analysis was 66% (95% CI: 51.2, 78.8; 33/50 patients). Median time to response is 8 cycles. For responders, 42.4% (14/33 patients) achieved response at cycle 5, 72.7% (24/33 patients) achieved response at cycle 9, 97% (32/33 patients) achieved response at cycle 13. Importantly, improvements in PN-related pain and motor impairment demonstrated that selumetinib provided clinical benefit. Selumetinib, therefore, has promising clinical activity for the treatment of NF1 and inoperable PN, as well as a favourable safety profile.

A detailed description of the chemistry, pharmacology, efficacy, and safety of selumetinib is provided in the Investigator's Brochure.

2.3 Benefit/risk assessment

2.3.1 Overall benefit/risk assessment

The primary objective of the study is to assess the safety, tolerability and PK of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN. As identified in the SPRINT study, selumetinib at a dose of 25 mg/m^2 had promising clinical activity for the treatment of NF1 and inoperable PN. In the phase I portion of the study, ORR was 66.7% (16/24 patients). The response rate was confirmed in SPRINT Phase II Stratum 1, in which the overall response rate by NCI POB central analysis was 66% (95% CI: 51.2, 78.8; 33/50 patients). Furthermore, responses were generally durable (median DoR based on NCI POB central analysis was not reached) and there was evidence of clinical benefit including improvement in pain and motor function. Selumetinib may therefore offer the potential for direct benefit in Chinese paediatric and adult subjects with NF1 and inoperable PN in terms of disease stabilisation or shrinkage, a reduction in tumour symptoms including pain, and improvements in health-related quality of life (HRQoL) and function. The primary risk to subjects participating in this study is from toxicity of selumetinib, an investigational agent. In the SPRINT study the most frequent adverse events (AEs; any grade) considered by the investigator to be possibly related to selumetinib at any dose in subjects with NF1 and inoperable PN included acneiform rash, asymptomatic creatine kinase (CK) elevation, and

gastrointestinal effects (abdominal pain, diarrhoea, nausea, and vomiting). AEs were predominantly mild/moderate in severity, predictable and manageable with standard clinical practice and generally did not affect the ability of subjects to remain on treatment.

The proposed exclusion criteria, safety monitoring, starting dose, toxicity management guidance and stopping criteria will minimise the risks for the subjects participating in this study. Additionally, AEs will be carefully monitored throughout the study.

The benefit/risk assessment for this study therefore appears to be acceptable for subjects for whom there is no alternative standard therapy.

2.3.2 Risks associated with selumetinib treatment

The following risks associated with selumetinib require specific monitoring and proposed guidance and algorithms for the management of these risks are described in Appendix E: Guidance for Management of Specific Adverse Events in Studies of Selumetinib. Refer to Section 8.4.5 and Appendix E for information on the management of AEs for subjects on selumetinib. The following situations require additional safety monitoring:

- All cardiorespiratory AEs with no obvious diagnosis should be assessed with a single electrocardiogram (ECG), echocardiogram, vital signs (resting blood pressure [BP], pulse rate), weight and blood samples for troponin (isoform per institution norm) taken at the time of the event.
- Ejection fraction decrease has been identified as a risk for selumetinib. Measurements of troponin (isoform per institution norm) and recording of a single ECG are to be performed when there is a significant drop in left ventricular ejection fraction (LVEF; decrease of $\geq$10 percentage points relative to baseline and to an absolute value LVEF below the institution's lower limit of normal [LLN] on study treatment) or any cardiorespiratory events with no obvious diagnosis. If there is not a defined institutional LLN, then the reference range as recommended by AstraZeneca should be applied. If troponin assessments are not available, per local practice, CK-MB isoform should be assessed. Subjects should be managed according to the algorithm provided Appendix E.
- All new dyspnoea AEs or worsening of pre-existing dyspnoea AEs should be investigated according to the algorithm provided in Appendix E.
- Visual disturbance; central serous retinopathy/retinal pigment epithelial detachment and retinal vein occlusion have been identified as risks for selumetinib. Regular monitoring of the eyes and conduct of specific ophthalmological examinations, including best corrected visual acuity, intraocular pressure (IOP) measurements, slit-lamp fundoscopy, optical coherence tomography and fundus photography have been included to enable prompt identification and management of visual disturbance symptoms, if required.

  - If a subject experiences an AE of visual disturbance (including blurring of vision) an ophthalmologic examination (including best corrected visual acuity, intraocular pressure, slit-lamp fundoscopy and with consideration of additional tests if clinically indicated [e.g. fundus photography if abnormality detected or optical coherence tomography scan]) must be performed and the AE managed according to Appendix E. In addition, ophthalmologic examinations may be performed at the discretion of the investigator, if clinically indicated.

- Specific guidance for AE management, interruption or reduction of treatment with selumetinib may be considered in the event of rash, stomatitis or diarrhoea, as indicated in the algorithms provided in Appendix E.
- Hyperphosphatemia and increases in calcium phosphate should be managed according to local practice.
- If unexplained muscle weakness or myalgia (muscle pain) occurs, the subject should have a neuromuscular examination, urine analysis and CK measurement performed (with an additional CK-MM isoform measurement where possible) and be managed according to local practice.

Regular monitoring of muscle symptoms and the conduct of specific tests, including a neuromuscular examination, urine analysis and measurements of blood levels of CK (and where possible, the CK-MM isoform), have been included in CSPs to enable prompt identification and management of symptoms if required. More detailed information about the known and expected benefits and risks and reasonably expected AEs of selumetinib may be found in the Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

Table 2 Study objectives

Primary objectives:	Endpoints:
To assess the safety and tolerability of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN	**Paediatric and adult cohorts:** Safety and tolerability will be evaluated in terms of AEs, clinical safety laboratory assessments, physical examination, vital signs, height/weight, ECG, echocardiogram, ophthalmologic assessment and performance status. **Paediatric only:** Safety and tolerability will also be evaluated in terms of bone growth and Tanner stages. **Assessments related to AEs will include:** • Occurrence/frequency. • Relationship to IP as assessed by investigator. • CTCAE grade. • Seriousness. • Death. • AEs leading to discontinuation of IP. • AEs of special interest.
To characterise the PK of selumetinib and its metabolite (N-desmethyl selumetinib) in Chinese paediatric and adult subjects with NF1 and inoperable PN	PK parameters for selumetinib and N-desmethyl selumetinib will be derived following single dose and multiple doses. These may include, but are not limited to: **After a single dose:** • AUC. • AUC_{0-12}. • AUC_{0-t}. • C_{max}. • t_{max}. • $t_{1/2}$. **After multiple doses:** • $AUC_{0-12,ss}$. • $C_{max,ss}$. • Rac.

Table 2 Study objectives

Secondary objectives:	**Endpoints:**
To evaluate the clinical efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN on ORR, DoR, PFS, TTP, and TTR	ORR is defined as the proportion of subjects who have a complete response or confirmed partial response (defined as a target PN volume decrease ≥20% compared to baseline, confirmed by a consecutive scan within 3 to 6 months after first response, as determined by the investigator and independent central review per Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. DoR is defined as the time from the date of first documented response (which is subsequently confirmed) until the date of documented progression or death in the absence of disease progression, as determined by the investigator and independent central review per REiNS criteria. PFS is defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review, or death due to any cause. TTP is defined as the time from the date of first dose until progression per REiNS criteria, as assessed by the investigator and independent central review. TTR is defined as the time from the date of first dose until the date of first documented response (which is subsequently confirmed), as determined by the investigator and independent central review per REiNS criteria.
To evaluate the effect of selumetinib on pain in Chinese paediatric and adult subjects with NF1 and inoperable PN	• FLACC scale (3 years of age). • Faces pain scale - revised (4 to 17 years of age). • NRS-11 (adult cohort). • PII (adult cohort; self- and parent-reported in the paediatric cohort). • Pain Medication Survey (self-reported in the adult cohort; parent-reported in the paediatric cohort).
To determine the effect of selumetinib on HRQoL	• PedsQL (paediatric cohort; self- and parent-reported). • EORTC QLQ-C30 and PlexiQoL (adult cohort).
To determine the effect of selumetinib on physical functioning	• PROMIS (upper extremity; self- and parent-reported in the paediatric cohort). • PROMIS (mobility; self- and parent-reported in the paediatric cohort). • PROMIS Physical Function - Short Form 8c 7-day (adult cohort).
Exploratory objectives:	**Endpoints:**
To evaluate PGIS of symptoms	• PGIS (adult cohort; self- and parent-reported in the paediatric cohort).

Table 2 Study objectives

To evaluate PGIC in symptoms	• PGIC (adult cohort; self- and parent-reported in the paediatric cohort).
To determine the effect of selumetinib on disfigurement	• Photographic evaluation.
Safety objective: contained within the primary objectives.	

AE=adverse event; AUC=area under the concentration-time curve from zero to infinity; AUC_{0-12}=area under the concentration-time curve from zero to 12 hours; $AUC_{0-12,ss}$=area under the concentration-time curve from zero to 12 hours at steady-state; AUC_{0-t}=area under the concentration-time curve from zero to the last measurable concentration; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum steady-state plasma concentration; CR=complete response; CTCAE=Common Terminology Criteria for Adverse Events; DoR=duration of response; ECG=electrocardiogram; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FLACC=Face, Legs, Activity, Cry, Consolability; HRQoL=health-related quality of life; IP=investigational product; NF1=neurofibromatosis type 1; NRS=Numeric Rating Scale; ORR=objective response rate; PedsQL=Paediatric Quality of Life Inventory; PFS=progression-free survival; PGIC=patient's global impression of change; PGIS=patient's global impression of severity; PII=Pain Interference Index; PK=pharmacokinetics; PlexiQoL=plexiform neurofibromas quality of life scale; PN=plexiform neurofibroma; PR=partial response; PROMIS=Patient-Reported Outcomes Measurement Information System; Rac=accumulation ratio; REiNS=Response Evaluation in Neurofibromatosis and Schwannomatosis; $t_{1/2}$=terminal half-life; t_{max}=time to maximum plasma concentration; TTP=time to progression; TTR=time to response.

4. STUDY DESIGN

4.1 Overall design

For an overview of the study design, see Figure 1. For details on treatments given during the study, see Section 6.1. For details on what is included in the efficacy and safety endpoints, see Section 3.

This is an open label Phase 1 study with 2 independent cohorts to assess the safety, tolerability, PK and clinical efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN. The primary objectives are to assess the safety, tolerability and PK of selumetinib in Chinese subjects with NF1 and inoperable PN and the secondary objectives are to assess the efficacy of selumetinib in Chinese subjects with NF1 and inoperable PN. The study population is subjects with a clinical diagnosis of NF1 per National Institutes of Health (NIH) guidelines (NIH Consensus Development Conference Statement 1988) and inoperable measurable PNs that require treatment due to symptoms or with the potential to develop significant clinical complications.

Approximately 16 paediatric and 16 adult subjects with NF1 and inoperable PN will be enrolled in the study. Assignment to the treatment cohort and evaluation of efficacy and safety will be performed independently for each cohort. The Safety Review Committee (SRC) will evaluate preliminary tolerability, safety and available PK data after the first 6 subjects have

been treated in both cohorts for approximately 3 cycles. Additional enrolment will be initiated per SRC recommendation. Detailed information will be provided in the SRC charter.

Screening tests should be performed within 28 days before the first administration of selumetinib, unless otherwise indicated. All subjects will have safety assessments (including haematology, chemistry and urinalysis safety panels) analysed at screening.

At the time of screening, PN will be classified by site (based on MRI assessment) as "typical PN" versus "nodular PN" versus "solitary nodular PN" as follows:

- Typical PN: Nodular component of PN is <30%
- Nodular PN: Nodular component of PN is ≥30%
- Solitary nodular PN: Whole body of the lesion is an encapsulated mass by MRI (Solitary nodular PN lesions cannot by selected as a target or non-target PN)

Subjects will be administered a single oral dose of selumetinib 25 mg/m^2 at Cycle 0 Day 1. During the following 2--day washout period, intensive PK samples will be collected before and after this first single dose until pre-dose at Cycle 1 Day 1. From Cycle 1 Day 1, subjects will be administered multiple doses of selumetinib 25 mg/m^2 twice daily (BID) on a continuous schedule (28 days per cycle). The dose of selumetinib will be capped at 50 mg when body surface area (BSA) is ≥1.9 m^2. Intensive PK samples will be collected on Cycle 1 Day 8 for assessment of the 12-hour PK profile at steady state. Subjects need to be hospitalised for intensive PK sampling during the single dose period (from Cycle 0 Day -1 to Cycle 0 Day 2) and on Cycle 1 Day 8 during the multiple dose period.

Subjects will continue to receive selumetinib until disease progression or unacceptable drug-related- toxicity, whichever occurs first. Selumetinib will be dispensed after all assessments have been performed and the next 28-day cycle will begin at that point. Subjects will therefore be required to attend the site monthly to receive selumetinib. Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses.

All subjects will be evaluated for safety and efficacy at a regular basis, as defined in Table 1.

Safety assessments (clinical chemistry, haematology, urinalysis, physical examination, vital signs, height and weight, ECG, echocardiogram, ophthalmologic assessment, Tanner stages and performance status) will be performed at screening and at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, as long as the subject remains on study treatment. Pregnancy tests will be performed at screening and at the end of each cycle. AEs will be collected from the time of signing the informed consent form (ICF), throughout the treatment

period and including the follow-up period. Safety assessments will also be performed at other visits during Cycles 0 and 1, as detailed in Table 1

Unless clinically indicated otherwise, tumour assessments, as measured by 3D volumetric magnetic resonance imaging (MRI) of the target and nontarget PN, will be obtained at screening and every 4 cycles (16±1 weeks) relative to the date of first dose for the first 2 years (24 cycles). From the end of Cycle 24, tumour assessments will be performed every 6 cycles (24±1 weeks) as long as the subject remains on study treatment or until disease progression. Disfigurement assessments will be performed at screening and then at the end of Cycles 8, 16 and 24 as long as the subject remains on study treatment.

Clinical outcome assessments will be performed at screening and at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, as long as the subject remains on study treatment.

An end of treatment visit will be performed for subjects who permanently discontinue study treatment for any reason (except for death, lost to follow-up or withdrawal of consent).

The 30-day safety follow-up visit will be conducted at 30 days post-last dose/end of treatment for both paediatric and adult cohorts. Long-term post-treatment safety follow-up assessments will be conducted for 1 year (at 6 and 12 months post-treatment) for paediatric subjects only.

For subjects who discontinue study treatment due to reasons other than disease progression, tumour assessments will continue for approximately 1 year, if clinically applicable, and the assessment schedule should continue per the regular tumour assessment interval.

To minimise bias, tumour assessments will be determined by independent central review according to Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria (PR defined as a PN volume decrease of ≥20% compared to baseline).

Refer to Table 1 for a comprehensive list of study assessments and their timings.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The

investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified Health Care Professional (HCP) or HCP provided by a third-party vendor (TPV) (where applicable).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices(where applicable).
- Home delivery of Selumetinib by a designated courier. If a site visit is not possible, Selumetinib may be delivered to the participant's home by a designated courier if feasible. The option of home delivery ensures a participant's safety in cases of a pandemic where participants may be at increased risk by travelling to the site/clinic. This will also minimize interruption of Selumetinib administration during other study disruptions, eg, site closures due to natural disaster.
- At-home Investigational Product (IP) administration: Performed by a site qualified HCP, HCP provided by a TPV or by the participants or the participant's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine(where applicable).

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix J.

4.2 Scientific rationale for study design

Selumetinib is an orally available, potent and selective, nonadenosine triphosphate-competitive MEK1/2 inhibitor. Since the NF1 protein is a negative regulator of

RAS, NF1 loss is associated with activation of RAS and the downstream signalling pathway. Therefore, inhibition of MEK, which lies downstream from RAS, blocks inappropriate signal transduction in the RAS-mitogen-activated protein kinase pathway and is anticipated to arrest tumour cell proliferation and growth, offering a promising antitumour therapeutic strategy. Nonclinical studies have demonstrated that selumetinib treatment can inhibit ERK phosphorylation and neurofibroma proliferation in mouse models of NF1.

This is the first study designed to evaluate the safety, tolerability, PK and efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN. A Phase 1 open label design was therefore considered to be appropriate for this study. The co-primary endpoints in this study will assess the safety, tolerability and PK of selumetinib in this subject population and the secondary endpoints will assess the efficacy of selumetinib. A comprehensive set of safety and efficacy measures will be assessed in this study, and PK will be assessed after both single and multiple doses. Tumour assessment will be performed according to REiNS criteria and determined by independent central review (PR defined as a PN volume decrease of ≥20% compared to baseline). The safety measures chosen and PK parameters to be assessed are standard for a Phase 1 study of this type.

The clinical outcome assessment methods used in this study are well-recognised and commonly used for assessing pain, HRQoL and physical functioning. The Face, Legs, Activity, Cry, Consolability (FLACC) scale (Merkel et al 1997) and Faces pain scale - revised (Hicks et al 2001), are well-recognised methods for assessing pain intensity in paediatric populations, and Numeric Rating Scale-11 (NRS-11; Hawker et al 2011; Dworkin et al 2005; Wolters et al 2013) is established for pain intensity assessments among adults. Pain Interference Index (PII; Wicksell et al 2009; Martin et al 2015) is a well recognised and commonly used method for assessing pain interference in children, and- has also been validated for adults (Kemani et al 2016). A pain medication survey is used to ensure that potential pain palliation is not the result of increased usage of analgesics (Basch et al 2014) and will be completed by all subjects.

The Paediatric Quality of Life Inventory (PedsQL) Core version 4 is a widely accepted measure for assessing HRQoL in paediatric subjects (Varni et al 2001) and will be used for the paediatric cohort. It has been developed in age-specific versions. In this study, the subject-reported versions are for subjects aged 5 to 7 years, 8 to 12 years, and 13 to 17 years. In addition, the corresponding parent-reported versions will also be included. For subjects 3 to 4 years of age, only the parent-reported version will be included. For the adult cohort, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; Aaronson et al 1993) and plexiform neurofibromas quality of life scale (PlexiQoL; Heaney et al 2019) will be used for assessments of HRQoL.

Patient-Reported Outcomes Measurement Information System (PROMIS) is a set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions (PROMIS website). The PROMIS Physical Functioning Scales have been validated in children (DeWitt et al 2011; Varni et al 2014). In this study, self-reported short forms will be administered to children from 8 to 17 years of age. Parallel parent proxy forms will be administered for children aged from 5 to 17 years. In the adult cohort, a newly developed PROMIS short form physical functioning scale will be used.

The patient's global impression of change (PGIC) instrument has been used in several research studies on chronic pain in adults and more recently in children (Arnold et al 2011; Mohammad et al 2014). It has been recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for clinical studies involving chronic pain (Dworkin et al 2005; McGrath et al 2008). The patient's global impression of severity (PGIS) instrument is used to measure a subject's global impression of symptom severity.

This study is supported by available clinical data from the ongoing SPRINT study in paediatric subjects with NF1 and inoperable PN (NCT01362803), an ongoing NCI-sponsored study in adults with NF1 and inoperable PN (NCT02407405), and clinical data of selumetinib in different tumour types.

In the clinical setting, treatment with selumetinib in the Phase 1 SPRINT study resulted in confirmed PRs (tumour volume decreases from baseline of ≥20%) in 16/24 (66.7%) children. The response rate was confirmed in the SPRINT Phase II Stratum 1 part of the study, for which the overall response rate by NCI POB central analysis was 66% (95% CI: 51.2, 78.8; 33/50 patients. Importantly, improvements in PN-related pain and motor impairment demonstrated that selumetinib provided clinical benefit. Selumetinib, therefore, has promising clinical activity for the treatment of NF1 and inoperable PN, as well as a favourable safety profile.

4.3 Justification for dose

In SPRINT Phase II Stratum 1, paediatric subjects with NF1 and inoperable PN (Study 8799; NCI 11-C-0161; SPRINT) received selumetinib at the recommended Phase II dose (25 mg/m^2 BID) with continuous dosing (1 cycle = 28 days). As reported in Clinical Study Report of Phase II Stratum 1 part of this study, 50 children (30 male; median age 10.2 years; range 3.5 to 17.4 years) were enrolled. As of 29 June 2018, NCI POB central analysis showed 33 (66.0%) patients had a best objective response of confirmed PR (target PN volume decrease ≥20% from baseline, confirmed by a consecutive scan within 3 to 6 months after first

response), 4 (8.0%) patients had an unconfirmed PR and 11 (22.0%) patients had stable disease; no patients had a best objective response of disease progression.

The PK properties of single dose selumetinib in healthy adult volunteers of Chinese, Japanese or other Asian descent were investigated in a study conducted in the United Kingdom (Study D1532C00086). Systemic exposure (area under the concentration-time curve from zero to infinity [AUC] and maximum plasma concentration [C_{max}]) of selumetinib in healthy volunteers of Asian (Chinese and Japanese data from Study D1532C00086) and Western (Study D1532C00066) descent were compared. Dose-normalised AUC and C_{max} of selumetinib in healthy adult Chinese subjects were approximately 1.4-fold higher than in Western subjects. However, minor differences were observed when comparing body weight- or BSA-normalised PK parameters. The geometric mean (G_{mean}) ratio (90% confidence intervals [CI]) of the dose- and body weight-normalised AUC and C_{max} between the Chinese and Western populations were 1.19 (1.03, 1.38) and 1.17 (0.92, 1.48), respectively. The G_{mean} ratio (90% CI) of the dose- and BSA-normalised C_{max} between Chinese and Western subjects were 1.29 (1.13, 1.47) and 1.26 (1.01, 1.59), respectively.

The exposure of Asian adult subjects from Study D1532C00086 was compared with the exposure of Western adult subjects from 9 studies (Studies D1532C00066, 69, 71, 78, 80, 81, 82, 83 and 85). On comparison of these data, it was found that the median AUC and C_{max} values were variable across studies for Western subjects; however, the overall distribution of exposure was in a similar range across the studies. The median AUC and C_{max} values in Chinese subjects were similar to those reported in Western subjects after body weight or BSA normalisation, and the distributions of individual values for AUC and C_{max} of selumetinib in Chinese subjects were within the distribution range of those in Western subjects.

Thus, a PK ethnic difference is not expected to be clinically relevant following a BSA-based dosing regimen, which will be implemented in the current Chinese Phase 1 PK study.

4.4 End of study definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit or last scheduled procedure as shown in Table 1.

Same DCOs would be applied for both analysis of pediatric cohort and adult cohort. Primary DCO in this study will take place when the last subject dosed has had the chance to complete their visit at the end of cycle 10. Final DCO will occur when the last subject dosed has had the chance to complete their visit at the end of cycle 24. In addition, an interim analysis will be conducted when last subject dosed has had the chance to complete their visit at the end of cycle 4 to assess PK, safety, tolerability and efficacy in Chinese subjects with NF1 and inoperable PN.

Subjects will be withdrawn from the study if the study is terminated. The study may be terminated if, in the judgment of AstraZeneca, study subjects are placed at undue risk because of clinically significant findings. In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, subjects currently receiving treatment with selumetinib may be transitioned to such a study, and the current study would terminate. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any subject who would be proposed to move to such a study would be given a new ICF to sign.

If selumetinib is approved locally and reimbursed for use in paediatric/adult patients with NF1 who have symptomatic, inoperable PN, participants should be switched to the commercial supply at the end of the study. However, if the participant is unable to access the commercial supply and they are still receiving clinical benefit, AstraZeneca and the Investigator will discuss how the participant could continue to receive selumetinib if he/she is benefiting from treatment.

See Appendix A 6 for guidelines for the dissemination of study results.

4.5 Safety Review Committee

An SRC will be established to perform a review of the safety, tolerability and PK (if available) of selumetinib treatment in this study.

The core members of the SRC consist of:

- Study physician, who will chair the committee, or delegate.
- Principal investigator or delegate from each investigational site that participates in the study.
- Global/local safety physician or delegate.
- Global clinical lead.

In addition, the study pharmacologist, study statistician and global study leader may also be invited as appropriate.

A separate document or remit will define the exact membership, role and responsibility (SRC charter).

Within each cohort, the SRC will evaluate preliminary tolerability, safety and available PK data after the first 6 subjects have been treated for approximately 3 cycles. Additional enrolment will be initiated per SRC recommendation. If necessary, further safety review committee meetings will be held. Detailed information will be provided in the SRC charter.

5. STUDY POPULATION

Subjects will be enrolled in China. Chinese subjects with a clinical diagnosis of NF1 (NIH Consensus Development Conference Statement 1988) and inoperable PN that require treatment due to symptoms or with the potential to develop significant clinical complications, as judged by the investigator, will be eligible.

Approximately 16 paediatric and 16 adult subjects with NF1-related and inoperable PN are expected to be recruited.

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be enrolled. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures (refer to Section 5.4).

For procedures for withdrawal of incorrectly enrolled subjects, see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria apply:

Informed consent

1 Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

Paediatric cohort: parent/legal guardian consent is required, where possible involving the paediatric subject in the assent process with appropriate documentation.

2 Provision of signed and dated written ICF prior to any mandatory study-specific procedures, sampling, and analyses.

Paediatric cohort: mandatory provision of signed and dated parent/legal guardian consent for the study along with the paediatric assent form, when applicable. For subjects who reach the age of legal consent during the clinical study, notification may be required and a new consent form may need to be signed by the subject.

The ICF process is described in Appendix A 3.

Age

3 Paediatric cohort: Chinese subjects ≥3 years and <18 years of age with a BSA ≥0.55 m^2 at the time of study enrolment who are able to swallow whole capsules. There must be a

minimum of 6 subjects each in the 3 to 11 and 12 to 17 year age groups at the time of enrolment.

Adult cohort: Chinese subjects ≥18 years of age at the time of study enrolment who are able to swallow whole capsules.

Disease diagnosis

4 All study subjects must be diagnosed with (i) NF1 per NIH Consensus Development Conference Statement 1988 and (ii) inoperable PN. In addition to PN, subjects must have at least 1 other diagnostic criterion for NF1 (NIH Consensus Development Conference Statement 1988):

- Six or more café-au-lait macules >5 mm in greatest diameter in pre-pubertal individuals and >15 mm in greatest diameter in post-pubertal individuals.
- Freckling in the axillary or inguinal regions.
- Optic glioma.
- Two or more Lisch nodules (iris hamartomas).
- A distinctive osseous lesion such as sphenoid dysplasia or tibial pseudarthrosis.
- A first-degree relative with NF1.

A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A histologic confirmation of the tumour is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant degeneration of a PN is clinically suspected.

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

5 Subjects' NF1 and inoperable PN require treatment due to actual symptoms or has the potential to develop significant clinical complications, as judged by the investigator, including but not limited to head and neck lesions that could compromise the airway or great vessels, paraspinal lesions that can cause myelopathy, brachial or lumbar plexus lesions that could cause nerve compression and loss of function, lesions that could result in major deformity (e.g. orbital lesions) or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.

6 Subjects must have at least one measurable typical or nodular PN, defined as a lesion of at least 3 cm measured in one dimension, which can be seen on at least 3 imaging slices and have a reasonably well-defined contour. Subjects who have undergone surgery for resection of a PN are eligible provided the PN was incompletely resected and is measurable. The target PN will be defined as the clinically most relevant PN,which has to be amenable to volumetric MRI analysis and classified as either typical or nodular (ie must not be solitary nodular).

7 Performance status: Subjects >16 years of age must have a Karnofsky performance level of ≥70, and children ≤16 years old must have a Lansky performance of ≥70 (Appendix G). Subjects who are wheelchair bound because of paralysis secondary to a PN should be considered ambulatory when they are in their wheelchair. Similarly, subjects with limited mobility secondary to a need for mechanical support (such as an airway PN requiring tracheostomy or continuous positive airway pressure) will also be considered ambulatory for the purpose of the study.

8 Adequate haematological function defined as absolute neutrophil count $\geq 1.5 \times 10^9$/L, haemoglobin ≥9g/dL, and platelet count $\geq 100 \times 10^9$/L. Subject must be without growth factor support and platelet transfusion support 7 days before the screening assessment.

9 Adequate organ function defined as follows: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2×upper limit of normal (ULN), total bilirubin ≤1.5×ULN except in the case of subjects with documented Gilbert's disease (≤2.5×ULN). Estimated creatinine clearance of ≥60 mL/minute, calculated using the formula of Cockcroft and Gault ([140 minus age] • mass [kg]/[72 • creatinine mg/dL] • multiply by 0.85 if female) or normal serum creatinine based on age, as described below:

Age (years)	Maximum creatinine (mg/dL)	Maximum creatinine (µmol/L)
≤5	0.8	70.7
5<age≤10	1.0	88.4
10<age≤15	1.2	106.1
>15	1.5	132.6

Reproduction

10 Negative pregnancy test (urine or serum) for female subjects of childbearing potential. A female of childbearing potential is defined as a subject 9 years of age and older or those showing pubertal development.

11 Female subjects with childbearing potential must be 1 year post-menopausal (amenorrhoeic for the past 12 months without an alternative medical cause), surgically sterile, or using an acceptable method of contraception for the duration of the study (from the time of signing consent) and for at least 4 weeks after the last dose of selumetinib to prevent pregnancy. An acceptable method of contraception is a combination of 2 methods, including but not limited to implants, injectables, combined oral contraceptives (e.g. the contraceptive pill), some intrauterine devices (e.g. placement of an intrauterine device or intrauterine system), and a male partner with sterilisation. True sexual abstinence is also an acceptable method of contraception. Reliable methods of contraception/birth control should be used consistently and correctly. The following age-specific requirements must also apply:

- Women <50 years old would be considered post-menopausal if they have been amenorrhoeic for the past 12 months or more following cessation of exogenous hormonal treatments. The levels of luteinising hormone and follicle-stimulating hormone must also be in the post-menopausal range.
- Women ≥50 years old would be considered post-menopausal if they have been amenorrhoeic for the past 12 months or more following cessation of all exogenous hormonal treatments, have had radiation-induced oophorectomy with the last menses >1 year ago, have had chemotherapy-induced menopause with >1 year interval since the last menses, or have had surgical sterilisation by either bilateral oophorectomy or hysterectomy.

12 Male subjects of reproductive potential must be surgically sterile by prior vasectomy or using an acceptable method of contraception (including use of condoms with spermicidal foams/gels or true abstinence) for the duration of the study (from the time they sign consent) and for at least 12 weeks after the last dose of study treatment to prevent pregnancy in a partner. Male subjects must not donate or bank sperm during this same time period.

5.2 Exclusion criteria

Subjects are eligible to be included in the study only if none of the following exclusion criteria apply:

1 Evidence of malignant peripheral nerve sheath tumour.

2 Prior malignancy (except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject had been disease free for ≥2 years or which would not have limited survival to <2 years) or other cancer requiring treatment with chemotherapy or radiation therapy. Note: these cases must have been discussed with the study physician.

3 A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of selumetinib, or put the study outcomes at undue risk.

4 Subjects with clinically significant cardiovascular disease as defined by the following:

- Known inherited coronary disease;
- BP:
  - For paediatric subjects, BP > the 95th percentile for age, height, and gender measured as described in (Appendix F).
  - Uncontrolled hypertension (at screening: BP ≥150/95 despite optimal therapy).
- Acute coronary syndrome within 6 months prior to starting treatment;

- Uncontrolled angina - Canadian Cardiovascular Society grade II to IV despite medical therapy (Appendix F);
- Symptomatic heart failure New York Heart Association Class II to IV, prior or current cardiomyopathy, or severe valvular heart disease (Appendix F);
- Prior or current cardiomyopathy including but not limited to the following:
  - Known hypertrophic cardiomyopathy.
  - Known arrhythmogenic right ventricular cardiomyopathy.
  - Previous moderate or severe impairment of LVEF <45% on echocardiogram or equivalent on multigated acquisition (MUGA) even if full recovery has occurred.
- Baseline LVEF below the LLN or <55% measured by echocardiogram or institution's LLN for MUGA;
- Severe valvular heart disease;
- Current or history of atrial fibrillation ;
- QT interval corrected by Fridericia's method (QTcF) >450 ms or other factors that increase the risk of QT prolongation.

5 Known history of human immunodeficiency virus, serologic status reflecting active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, or any uncontrolled active systemic infection:

- Subjects who are hepatitis B core antibody positive and who are surface antigen (HBsAg) negative will need to have a negative HBV deoxyribonucleic acid polymerase chain reaction (PCR) result before enrolment. Subjects who are HBsAg positive or hepatitis B PCR positive will be excluded;
- Subjects who are hepatitis C antibody positive will need to have a negative HCV ribonucleic acid PCR result before enrolment. Those who are hepatitis C PCR positive will be excluded.

6 Subjects with the following ophthalmological findings/conditions:

- Current or past history of retinal pigment epithelial detachment/central serous retinopathy or retinal vein occlusion;
- Intraocular pressure >21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP). Subjects with known glaucoma and increased IOP who do not have meaningful vision (light perception only or no light perception) and are not experiencing pain related to the glaucoma, may be eligible after discussion with the study physician.
- Any other significant abnormality on ophthalmic examination that would make the subject unsuitable for enrolment into the study, as assessed by the investigator.

- Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or longstanding orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study.

7 Have received or are receiving an investigational medicinal product (IMP) or other systemic PN target treatment (including chemotherapy, hormonal therapy, radiation therapy, immunotherapy or biologic therapy) within 4 weeks prior to the first dose of study treatment, or within a period during which the IMP or systemic PN target treatment has not been cleared from the body (e.g. a period of 5 'half-lives'), whichever is the most appropriate and as judged by the investigator.

8 Inability to undergo MRI and/or contraindication for MRI (i.e. prosthesis or orthopaedic or dental braces that would interfere with volumetric analysis of target PN on MRI).

9 Have refractory nausea and vomiting, chronic gastrointestinal diseases (e.g. inflammatory bowel disease), or significant bowel resection that would adversely affect the absorption/bioavailability of the orally administered study medication.

10 Have had prior treatment with a MEK, Ras or Raf inhibitor (including, but not limited to, vemurafenib).

11 Supplementation with vitamin E greater than 100% of the daily recommended dose. Any multivitamin containing vitamin E must be stopped prior to initiation of selumetinib.

12 Receiving herbal supplements or medications known to be strong inhibitors or inducers of the cytochrome P450 (CYP)2C19 and CYP3A4 enzymes unless such products can be safely discontinued at least 14 days before the first dose of study medication.

13 Have any unresolved chronic toxicity *except alopecia* with Common Terminology Criteria for Adverse Events (CTCAE) grade ≥2, from previous anticancer therapy including radiation.

14 Have had recent major surgery within a minimum of 4 weeks prior to starting study treatment, with the exception of surgical placement for vascular access. Have planned major surgery during the treatment period.

15 Known severe hypersensitivity to selumetinib or any excipient in the selumetinib formulation, or history of allergic reactions attributed to compounds of similar chemical or biologic composition to selumetinib.

16 Breastfeeding or pregnant (it is allowed to discontinue lactation and participate in the study; however, resumption of lactation after study completion is not allowed).

17 Have evidence of any other significant clinical disorder or laboratory finding that, as judged by the investigator, makes it undesirable for the subject to participate in the study.

18 Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

Selumetinib capsules should be swallowed whole with a glassful of water twice a day, approximately 12 hours apart, on an empty stomach (no food or drink other than water for 2 hours prior to dosing and 1 hour after dosing).

During the study, subjects should avoid consuming large amounts of grapefruits, Seville oranges, or any other products that may contain these fruits (e.g. grapefruit juice) as these may affect selumetinib metabolism.

5.3.2 Activity

Subjects should avoid donating blood whilst participating in studies of selumetinib and for at least 12 weeks after receiving the last dose of selumetinib, or for longer if required.

Subjects should be made aware of the need for good oral care during studies with selumetinib (Appendix E).

5.3.3 Other restrictions

Whenever subjects are confined in the ward during the intensive PK sampling period, only the drinks and meals provided by the study personnel will be allowed. It is important that all meals are consumed as scheduled and that the meals in each period are exactly the same.

Intake of alcohol will not be allowed 72 hours prior to admission and until completion of PK sample collection.

5.4 Screen failures

Screen failures are defined as subjects who signed the ICF to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

These subjects should have the reason for study withdrawal recorded as “eligibility criteria not fulfilled” (i.e. the subject does not meet the required inclusion or exclusion criteria). This reason for study withdrawal is only valid for screen failures. Subjects may be rescreened once if the screening failure was due to a temporary condition. Any rescreening of subjects must be done in consultation with the AstraZeneca study physician and any decision must be captured in the subject’s medical notes.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. Study intervention in this study refers to selumetinib.

6.1 Treatments administered

6.1.1 Investigational products

Table 3 Study treatments

	Treatment
Study treatment name:	Selumetinib
Dosage formulation:	10 mg and 25 mg capsules
Route of administration:	Oral
Dosing instructions:	All eligible subjects will first receive a single oral dose of selumetinib 25 mg/m^2. After a washout period of 2 days, oral selumetinib 25 mg/m^2 BID (approximately every 12 hours) will be administered continuously for 28-day cycles with no rest periods between cycles. Subjects should be instructed to take the dose of selumetinib on an empty stomach (no food or drink other than water for 2 hours before and 1 hour after dosing) with water only. The capsules cannot be crushed and must be swallowed whole. Dosing will be performed based on BSA calculated by the equation below, and doses will be rounded to the nearest 5 to 10 mg using a dosing nomogram (Table 4). BSA should be calculated at screening and every tumour assessment visit. The dose of selumetinib will be capped at 50 mg when BSA is ≥1.9 m^2. At follow-up evaluations during tumour assessment visits, the dose of selumetinib will be adjusted for changes in BSA according to the dosing nomogram. For paediatric subjects with a body weight ≤30 kg: BSA (m^2) = body weight (kg) × 0.035 + 0.1 For paediatric subjects with a body weight ≥30 kg: BSA (m^2) = 1.15 + (body weight [kg] - 30) × 0.02 For all adult subjects: BSA (m^2) = 0.0061 × height (cm) + 0.0128 × body weight (kg) - 0.01529 Subjects will continue to receive selumetinib until disease progression or unacceptable drug-related toxicity, whichever occurs first. If a dose of selumetinib is missed, it should only be taken if it is more than 6 hours until the next scheduled dose. Do not take an additional dose if vomiting occurs after selumetinib administration but continue with the next scheduled dose.

Packaging and labelling:	Study treatment will be supplied as 10 mg (white) and 25 mg (blue) capsules in 60 count bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with Good Clinical Practice Ordinance. Details are specified in the document "explaining the reconstitution procedures and other handling procedures for the investigational products".
Provider:	AstraZeneca

BID=twice daily; BSA=body surface area.

Table 4 Dosing nomogram for the selumetinib PK study

25 mg/m^2	BSA (m^2)	0.55 to 0.69	0.7 to 0.89	0.9 to 1.09	1.1 to 1.29	1.3 to 1.49	1.5 to 1.69	1.7 to 1.89	≥1.9
	Dose[a] AM (mg)	20	20	25	30	35	40	45	50
	Dose[a] PM (mg)	10	20	25	30	35	40	45	50

BID=twice daily; BSA=body surface area.
[a] Actual dose in mg (capsule sizes 10 and 25 mg) administered BID approximately every 12 hours.

6.2 Preparation/handling/storage/accountability

AstraZeneca will supply selumetinib 10 mg (white) and 25 mg (blue) capsules in 60 count bottles to the investigator sites. These bottles will be dispensed to subjects in the AstraZeneca packing provided at the study site on treatment visits and within visit windows as specified in Table 1.

Selumetinib should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified in the document "explaining the reconstitution procedures and other handling procedures for the investigational products".

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies must be reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the drug handling instruction.

6.3 Measures to minimise bias: randomisation and blinding

6.3.1 Subject enrolment and randomisation

This is an open label Phase 1 study to assess the safety, tolerability, PK, and clinical efficacy of selumetinib in Chinese paediatric and adult subjects with NF1 and inoperable PN. Randomisation will not be performed in this open label study. Approximately 16 paediatric and 16 adult subjects with NF1 and inoperable PN will be enrolled in the study. Enrolment and treatment assignment will be performed using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS).

The investigator(s) will:

1 Obtain signed informed consent from the potential subject/parent or guardian of paediatric subject before any study specific procedures are performed.
2 Obtain a unique 7-digit enrolment number (E-code), through the IVRS/IWRS in the following format (ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the subject enrolment code at the centre). This number is the subject's unique identifier and is used to identify the subject on the electronic case report forms (eCRFs).
3 Determine subject eligibility (see Section 5.1 and Section 5.2 for inclusion and exclusion criteria, respectively).

At Cycle 0 Day 1, once the subject is confirmed to be eligible, the investigator, or suitably trained delegate, will:

1. Call IVRS/IWRS for treatment assignment or registration.
2. Subjects may be enrolled but not treated. If the subject is not treated, the IVRS/IWRS should be contacted to terminate the subject in the system.
3. The IVRS/IWRS will be used to track drug supply.

Subjects may be rescreened once if the screening failure was due to a temporary condition. Any rescreening of subjects must be done in consultation with the AstraZeneca study physician and any decision must be captured in the subject's medical notes.

If a subject withdraws from the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced.

6.3.2 Methods for ensuring blinding

This is an open label study; no blinding methods will be applied.

Procedures for handling subjects incorrectly started on treatment are as follows:

- Subjects who fail to meet the eligibility criteria should not, under any circumstances, receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.
- Where a subject does not meet all the eligibility criteria but is incorrectly started on treatment, the investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the subject.

6.4 Treatment compliance

The administration of all study treatments should be recorded in the appropriate section of the eCRF. The study treatment provided for this study will be used only as directed in this CSP.

Subjects will receive a drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Subject compliance will be assessed at each study visit as outlined in Table 1. Any change from the dosing schedule, including dose interruptions, dose reductions, and dose discontinuations should be recorded in the eCRF.

A treatment visit can be rescheduled within the visit window.

The IP Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP and for ensuring that the subject has returned all unused IP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Table 5 Restricted medications

Medication/class of drug	Usage (including limits for duration permitted and special situations in which it is allowed)
Any investigational anticancer therapy other than that under investigation in this study.	Should not be given concomitantly whilst the subject is on study treatment.

Unless considered to be clinically indicated, subjects should avoid taking other additional nonstudy medications that may interfere with the study medication. Strong or moderate inducers of CYP3A4 as well as strong or moderate inhibitors of CYP3A4 or CYP2C19 are not recommended at any time during the study. During the first cycle concomitant use of strong or moderate inhibitors of CYP3A4 or CYP2C19 should be avoided until after the PK assessment. During the remainder of the study, if concomitant use of selumetinib with strong or moderate CYP3A4 or CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Table 31and the patient should be monitored closely for potential toxicities. The dose of selumetinib should be reduced for the duration of concomitant therapy with the strong or moderate CYP3A4 or CYP2C19 inhibitor. After the washout for 5 half-lives of the inhibitor is complete, the selumetinib dose can be re-escalated. Refer to Appendix H for more detail.

Selumetinib capsules contain vitamin E in the form of D-α-tocopheryl polyethylene glycol 1000 succinate, a water-soluble form of vitamin E which acts as a formulation excipient. The maximum daily dose of vitamin E that a study subject may receive from selumetinib is approximately 261.6 mg/day. Therefore, subjects should not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interfere with blood coagulation processes.

Selumetinib should be administered with caution in subjects who are also receiving concomitant coumarin anticoagulant medications (e.g. warfarin). These subjects should have their international normalised ratio monitored/anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

Table 6 Prohibited medications

Prohibited medication/class of drug	Usage (including limits for duration permitted and special situations in which it is allowed)
Other IMP	Not allowed for 4 weeks or 5 half-lives (whichever is more appropriate as judged by the investigator) prior to the first dose of study treatment.
MEK, Ras or Raf inhibitor	Prior treatment is prohibited.
Other systemic PN target treatment (including chemotherapy, hormonal therapy, radiation therapy, immunotherapy or biologic therapy)	Not allowed for 4 weeks or 5 half-lives (whichever is more appropriate as judged by the investigator) prior to the first dose of study treatment.
Multivitamins containing vitamin E	Must be stopped prior to initiation of selumetinib.
Herbal supplements or medications known to be strong or moderate inducers of CYP3A4, or strong or moderate inhibitors of CYP3A4 and CYP2C19 (Appendix H)	Must be safely discontinued at least 14 days before the first dose of study medication. Strong or moderate inducers of CYP3A4 are not allowed at any time during the study. Concomitant use of strong or moderate inhibitors of CYP3A4 and CYP2C19 should be avoided until after the PK assessment on Cycle 1 Day 8. During the remainder of the study (i.e. from Cycle 1 Day 9 onwards), if concomitant use of strong or moderate CYP3A4 and CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Appendix H.

CYP=cytochrome P450; IMP=investigational medicinal product; MEK=mitogen activated protein kinase kinase.

Pain medication usage will be analysed separately (see Section 8.1.3.1.5).

6.5.1 Background medication

Not applicable.

6.5.2 Other concomitant treatment

Medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

A pain medication survey will be implemented as discussed in Section 8.1.3.1.5.

6.5.3 Rescue medication

Not applicable.

6.6 Dose modification and discontinuation

Specific guidance for the management of AEs, including interruption or reduction of treatment with selumetinib, may be considered for particular events of special interest (i.e. diarrhoea, dyspnoea, rash, asymptomatic reduction in LVEF, and visual disturbance), as indicated in the algorithms provided in Appendix E. Oral care recommendations are also provided in Appendix E. Some AEs (hyperphosphatemia and increase in calcium phosphate) should be managed according to local practice.

For all AEs reported in this study that are considered at least partly related to administration of selumetinib, the following dose reduction/adjustment guidance should be applied unless otherwise specified in the Guidance for management of specific AE (Appendix E):

- Treatment with selumetinib should be temporarily interrupted if one of the following AEs occurs and is considered related to treatment with selumetinib:
  - Any intolerable AE regardless of grade.
  - Any AE CTCAE grade 3.

  On improvement of the AE to CTCAE grade 1 or less within 4 weeks of onset, study treatment may be restarted at a reduced dose at the discretion of the investigator. Two-step dose modification is applied in the study (see Table 7). Any subjects with 2 prior dose reductions who experience a toxicity that would cause a third dose reduction must be discontinued from study treatment.

Table 7 Two-step Dose Modification Procedure

Body surface area (m^2)	Selumetinib dose (mg)[a] Dose level 0		First selumetinib dose (mg) reduction		Second selumetinib dose (mg) reduction[b]	
	AM	PM	AM	PM	AM	PM
0.55 to 0.69	20	10	10	10	10 mg once daily	
0.7 to 0.89	20	20	20	10	10	10
0.9 to 1.09	25	25	25	10	10	10
1.1 to 1.29	30	30	25	20	20	10
1.3 to 1.49	35	35	25	25	25	10
1.5 to 1.69	40	40	30	30	25	20
1.7 to 1.89	45	45	35	30	25	20
≥1.9	50	50	35	35	25	25

[a] Actual dose in mg (capsule sizes 10 and 25 mg) administered every 12 hours to achieve a dosage of 25 mg/m^2 twice daily.
[b] Permanently discontinue selumetinib in patients unable to tolerate Selumetinib after two dose reductions.

- If a different AE subsequently requires dose interruption, appropriate selumetinib dose modification should be considered on improvement of the AE at the discretion of the investigator, in line with Table 7.
- The dose may be increased to account for an increase in BSA at the time of on study evaluations.

Treatment with selumetinib should be permanently discontinued for any CTCAE grade 4 toxicity that is at least partially related to selumetinib. However, if it is felt to be in the best interest of the subject, interruption of Selumetinib with potential to restart at a reduced dose upon resolution to grade 1 or less may be considered on a case-by-case basis for CTCAE grade 4 AEs in consultation with the study physician.

6.7 Treatment after the end of the study

The investigator will discuss available treatment options with subjects who complete the study or who withdraw from the study early.

Subjects who continue to receive benefit from selumetinib at the final DCO and database closure may continue to receive selumetinib for as long as the investigator feels they are gaining clinical benefit. For subjects continuing to receive selumetinib treatment following the final DCO and database closure, it is recommended that the subject continues attending the scheduled site visits and the investigator continues to monitor the subject's safety laboratory results prior to and periodically during treatment with selumetinib in order to manage AEs.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, subjects currently receiving treatment with selumetinib may be transitioned to such a study, and the current study would terminate. The roll-over or safety extension study would ensure treatment continuation with visit assessments per its protocol. Any subject that would be proposed to move to such study would be required to sign a new ICF.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

See Table 1 for data to be collected at the time of treatment discontinuation and follow-up, and for any further evaluations that need to be completed.

Subjects may discontinue study treatment in the following situations.

- Subject decision. The subject or parent(s)/legal guardian is free to discontinue study treatment at any time without prejudice to further treatment. A subject who discontinues study treatment is normally expected to continue to participate in the study (e.g. for safety follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (Section 7.3).
- AE that in the opinion of the investigator or AstraZeneca contraindicates further dosing.
- Pregnancy or intent to become pregnant.
- Severe noncompliance with the CSP that, in the opinion of the investigator or AstraZeneca, warrants withdrawal from treatment with IP (e.g. refusal to adhere to scheduled visits).
- Initiation of alternative anticancer therapy including another IMP.
- Subjects who experience a PR and in whom the target PN becomes amenable to surgery.
- Subjects who experience disease progression.

  Subjects who achieved a PR of their PN and have subsequently had PN regrowth that meets the criteria for disease progression (≥20% increase from best response) may be permitted to remain on study treatment as long as their PN remains less than 20% above baseline volume and they are receiving clinical benefit in the absence of significant toxicity. These patients will still be considered to have progressive disease for the purpose of analysis of the trial endpoints. PN volume assessments will continue as described in the schedule of assessments and if PN volume increases to ≥20% above baseline, study treatment will be discontinued.
- It is deemed in the best interest of the patient, in this instance the sponsor should be notified and the reasons for discontinuation should be noted in the CRF.

Please note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

7.1.1 Temporary discontinuation

Dosing can be interrupted due to AEs or unforeseen circumstances as described in Section 6.6.

7.1.2 Rechallenge

Dosing may be restarted following interruption as described in Section 6.6.

7.1.3 Procedures for discontinuation of study treatment

Subjects or his/her parent(s)/legal guardian are free to discontinue IP or withdraw from the study at any time without prejudice to further treatment. Procedures to follow for study withdrawal are detailed below.

The investigator should instruct the subject or his/her parent(s)/legal guardian to contact the site before or at the time study treatment is stopped. A subject or his/her parent(s)/legal guardian who decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. All study treatment should be returned by the subject at their next on-site study visit or unscheduled visit. Subjects permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the investigator.

Discontinuation of study treatment, for any reason, does not impact on the subject´s participation in the study. The subject should continue attending subsequent study visits and data collection should continue according to the study protocol. Subjects who discontinue study treatment due to reasons other than disease progression will continue to undergo tumour assessments for approximately 1 year, if clinically applicable, and the assessment schedule should continue per the regular tumour assessment interval. If the subject or his/her parent(s)/legal guardian does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This could be a telephone contact with the subject or his/her parent(s)/legal guardian, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A subject or his/her parent(s)/legal guardian who agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Subjects who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Subjects who are permanently discontinued from study treatment will enter follow-up (see Table 1). Subjects who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if they fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the study site for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject or next of kin (e.g. by repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study, the subject should be considered to be lost to follow-up with unknown vital status at the end of the study and censored at the latest follow-up contact.

7.3 Withdrawal from the study

A subject may withdraw from the study (e.g. withdraw consent), at any time (IP **and** assessments) at his/her own request, without prejudice to further treatment.

A subject who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g. telephone contact, a contact with a relative or treating physician, or information from medical records) per Section 7.1.3.

If the subject or his/her parent(s)/legal guardian withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject or his/her parent(s)/legal guardian withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The investigator will follow up subjects as medically indicated.

AstraZeneca or its delegate will request investigators to collect information on subjects' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status at the end of the study for all subjects is crucial for the integrity of the study.

See Table 1 for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All study treatment and treatment diaries should be returned by the subject.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in Table 1.

The investigator will ensure that data are recorded in the eCRFs. The Web Based Data Capture (WBDC) system will be used for data collection and query handling.

The investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in Table 1, is essential and required for the conduct of the study.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all of the eligibility criteria. The investigator will maintain a screening log to record details of all screened subjects and to confirm eligibility or record the reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g. blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in Table 1.

Repeated or unscheduled samples may be taken for safety reasons or due to technical issues with the samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in Table 1.

8.1.1 Tumour response

In 2013, consensus recommendations for the imaging of PN were issued by an international working group (REiNS) who recommended MRI volumetric tumour assessment as preferable to all other MRI analysis techniques. MRI with volumetric analysis is recommended to sensitively and reproducibly evaluate changes in tumour size in clinical studies. Volumetric analysis requires adherence to specific imaging recommendations and a 20% volume change was chosen to indicate a decrease or increase in tumour size.

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging Contract Research Organization (CRO) for QC, storage, and for Independent Central Review (ICR). The details about target lesion location and non-target lesion location (if relevant) will also be collected to insure the independent reviewer also follow the most clinically relevant PN. Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from the sites to the CRO is strongly encouraged. An independent central review of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator tumor assessments will not be shared with the central reviewers. The management of patients will be based upon the results of the tumor assessments conducted by the Investigator.

Extent of PN in patients with NF1 can be very substantial, and may not allow for all lesions to be followed using 3D-MRI. Prior to starting treatment on this study, the investigator must select the target PN. The target PN defined as the most clinically relevant PN that is also measurable and either typical or nodular (ie not a solitary nodular lesion). If there is a second PN that is also considered clinically relevant, the investigator may select this as a non-target lesion; only one non-target lesion can be selected. Non-target lesions must also be measurable and either typical or nodular. Both the investigator and AstraZeneca-appointed imaging Contract Research Organization (CRO) will measure the target PN and non-target PN (if applicable).

A site imaging specialist will be appointed and trained on performing the assessments for the study.

Screening imaging evaluation:

- Identify and select the inoperable target PN (plus a maximum of 1 additional nontarget PN) for 3D MRI evaluation . Should there be more than 2 inoperable PNs that meet the criteria for selection, the 2 most clinically relevant PNs will be followed by 3D MRI analysis.
- Perform MRI sequences on the selected index lesions as outlined in the MRI acquisition protocols.

On study imaging evaluation:

Unless clinically indicated otherwise, and as defined in Table 1, 3D volumetric MRI of the target and nontarget PNs should be performed at every 4 cycles (16±1 weeks) relative to the date of first dose for the first 2 years (24 cycles). From the end of Cycle 24, tumour assessments will be performed every 6 cycles (24±1 weeks), as long as the subject remains on study treatment or until disease progression. Subjects who discontinue study treatment due to reasons other than disease progression will continue to undergo tumour assessments for

approximately 1 year, if clinically applicable, and the assessment schedule should continue per the regular tumour assessment interval.

- Complete response (CR): disappearance of the target lesion.
- PR: decrease in the volume of the target PN by 20% or more compared to baseline. The PR is considered unconfirmed at the first detection and confirmed when observed again at a consecutive scan within 3 to 6 months.
- Stable disease: insufficient volume change to qualify for either PR or PD.
- PD: increase in the volume of the target PN by 20% or more compared to baseline or the time of best response after documenting a PR. The appearance of new PN (with the exception of new discrete subcutaneous neurofibromas as noted below) or unequivocal progression of an existing nontarget PN is also considered PD. In this study unequivocal progression is defined as an increase in the volume of the non-target PN by 20% or more compared to baseline.

The clinical appearance of new discrete subcutaneous neurofibromas does not qualify for disease progression. Worsening of existing symptoms or the appearance of new symptoms that persist for more than 7 days and that are felt to be definitely related to the PN should be evaluated by repeating the MRI. Subjects should not be classified as having PD solely on the basis of new or increased symptoms

Some subjects may have incomplete MRI scans during the follow-up visits and this has the potential to lead to partial volume measurements, which may not be consistent with the baseline measurements. As such, further information on how to approach these partial volumes will be provided in the site imaging analysis guideline.

Subjects who have completed any protocol-derived therapy (as little as 1 dose) will be considered evaluable for response.

Subjects who discontinue study treatment due to reasons other than disease progression will continue tumour assessments for approximately 1 year, if clinically applicable.

8.1.2 Disfigurement

Consenting subjects will have photographic documentation of visible PNs according to Table 1. Photography should be performed at screening and then at the end of Cycles 8, 16 and 24 as long as the subject remains on treatment. All photographs at each time point should be taken from the same distance, if possible using similar lighting and camera settings. Baseline photographs should be present at the time of follow-up photography to allow for the best possible comparison.

Detailed recommendations for photography techniques are provided in the photography manual.

8.1.3 Clinical outcome assessments (COAs)

COAs, an umbrella term referring to all outcomes and symptoms, can be reported directly by the subject (patient-reported outcomes), by a clinician (clinician-reported outcomes) or by an observer (observer-reported outcomes). In the current study, both patient-reported outcomes and observer-reported outcomes will be used. COA will be measured in accordance with Table 1. Copies of each of the assessments used are included in Appendix I.

Baseline clinical outcome assessments should be performed prior to and as close to the first dose of selumetinib as possible (PGIC should not have any baseline assessments). Post-baseline assessments should be performed at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, as long as the subject remains on study treatment. Clinical outcome assessments will be performed electronically using on-site tablets.

Table 8 Overview of eligible subjects completing clinical outcome assessment questionnaires, by age of patient and respondent

Clinical outcome evaluation questionnaire	Respondent	Relevant PN morbidity at enrolment	Age
FLACC	Parent/guardian-reported	All PN	3 years
Faces pain scale	Self-reported	All PN	4 to 17 years
NRS-11	Self-reported	All PN	Adults
PII	Self-reported Parent/guardian-reported	All PN	8 to 17 years Adults 5 to 17 years
Pain medication survey	Self-reported on paper in the adult cohort and Parent/guardian-reported on paper in the paediatric cohort	All PN	All subjects
PedsQL	Self-reported Parent/guardian-reported	All PN	5 to 7 years 8 to 12 years 13 to 17 years 3 to 4 years 5 to 7 years 8 to 12 years 13 to 17 years
EORTC QLQ-C30	Self-reported	All PN	Adults

Table 8 Overview of eligible subjects completing clinical outcome assessment questionnaires, by age of patient and respondent

Clinical outcome evaluation questionnaire	Respondent	Relevant PN morbidity at enrolment	Age
PlexiQoL	Self-reported	All PN	Adults
PROMIS (mobility)	Self-reported Parent/guardian-reported	All PN	8 to 17 years 5 to 17 years
PROMIS (upper extremity function)	Self-reported Parent/guardian-reported	All PN	8 to 17 years 5 to 17 years
PROMIS (Physical Function – Short Form 8c 7-day)	Self-reported	All PN	Adults
PGIS	Self-reported Parent/guardian-reported	All PN	8 to 17 years Adults Up to 17 years
PGIC	Self-reported Parent/guardian-reported	All PN	8 to 17 years Adults Up to 17 years

EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FLACC=Face, Legs, Activity, Cry, Consolability; NRS=Numeric Rating Scale; PedsQL=Paediatric Quality of Life Inventory; PGIC=patient's global impression of change; PGIS=patient's global impression of severity; PII=Pain Interference Index; PlexiQoL=plexiform neurofibromas quality of life scale; PN=plexiform neurofibroma; PROMIS=Patient-Reported Outcomes Measurement Information System.

8.1.3.1 Pain

The effect of selumetinib on pain will be evaluated using the FLACC scale (children aged 3 years), Faces pain scale - revised (children aged 4 to 17 years), NRS-11 (adult cohort only), PII (adult cohort; self- and parent-reported in the paediatric cohort) and pain medication survey (all subjects).

8.1.3.1.1 FLACC pain scale (3 years)

The FLACC scale is an observer-reported measurement used to assess pain in children aged from 2 months to 7 years, or for individuals that are unable to communicate their pain. In this study, parents will receive a short training on how to do the assessments of pain for their child. The scale is scored from 0 to 10, with 0 representing no pain. The scale has 5 criteria (face, legs, activity, cry, and consolability), which each are assigned a score of 0 to 2 (Merkel et al 1997). In this study, the FLACC scale will be used to assess pain in children 3 years of age.

8.1.3.1.2 Faces pain scale - revised (4 to 17 years)

The Faces pain scale - revised is a self-reported measure of pain intensity developed for children. Facial images depicting no pain (score of 0) to very much pain (score of 10) are

presented to the child, who will then pick the face that matches their own discomfort over the past week, giving a score. The scale shows a close linear relationship with visual analog pain scales across the age range of 4 to 16 years. It is easy to administer and requires no equipment except for the photocopied faces (Hicks et al 2001). In this study, the Faces pain scale will be used to assess pain in children aged from 4 to 17 years of age. If subjects have difficulties reading, it is permissible for site staff to read the instructions to the subject and point to the faces as they read the instructions. If a subject has difficulties remembering the worst pain they had the past week, instructions should be given to assess the worst pain they had today.

8.1.3.1.3 NRS-11 (adult cohort only)

The NRS-11 is a self-reported segmented 11-point numeric scale that assesses pain intensity (Hawker et al 2011). It consists of a horizontal line with 0 representing "no pain" at the left end of the line and 10 representing "worst pain you can imagine" at the right end. Subjects are asked to select the one number from 0 to 10 that best describes their worst pain over the past 7 days for the following: 1) physician selected target-tumour pain, 2) overall tumour pain, and 3) overall pain. It takes less than 1 minute to complete. The target tumour will be selected by the physician from a list of body locations in Table 9. The NRS-11 is recommended as a core outcome measure of pain intensity for clinical studies (Dworkin et al 2005; Wolters et al 2013). Adult subjects only will complete the NRS-11 for this study.

Table 9 List of body locations

1	Head	16	Pelvic area
2	Eye	17	Genitalia
3	Face	18	Upper arm
4	Ear	19	Forearm
5	Mouth/Tough	20	Hand
6	Neck (Front)	21	Thigh/Upper leg
7	Neck (Back)	22	Lower leg
8	Shoulder	23	Foot
9	Chest		
10	Armpit		
11	Flank		
12	Back (Upper)		
13	Back (Lower)		
14	Abdomen		
15	Buttock		

8.1.3.1.4 Pain Interference Index

The PII is a 6-item measure that assesses the degree to which pain has interfered with daily activities in the past week. This measure was developed in Sweden and validated in Swedish with a group of children and adolescents with longstanding idiopathic pain (Wicksell et al 2009). The PII was translated into English and the wording was modified to make it more readable and to shorten the time frame to 1 week. A parallel parent version of the PII was also created. Results of validation studies in children with NF1 and their parents indicate that the internal consistency and construct validity of the PII are good. These data support the use of the PII to assess pain interference in youths with NF1 and PNs (Martin et al 2015). PII has also been validated for use in adults (Kemani et al 2016). For this study, adults and children from 8 to 17 years of age will complete self-reported PII, and parents or the legal guardian of children from 5 to 17 years of age will complete the parent proxy PII.

8.1.3.1.5 Pain medication survey (all subjects)

A pain medication survey will be used to ensure that potential pain palliation is not the result of increased usage of analgesics (Basch et al 2014). Information on daily and as-needed pain medications will be collected, including dates, pain medication name, dose and frequency. The pain medication survey will not be collected through the eCOA tablet, but with a paper version.

8.1.3.2 Health-related quality of life

The effect of selumetinib on HRQoL will be evaluated using the PedsQL (paediatric cohort) and EORTC QLQ-C30 and PlexiQoL (adult cohort).

8.1.3.2.1 PedsQL (paediatric cohort)

The PedsQL Core version 4 is a widely accepted measure for assessing HRQoL in paediatric subjects (Varni et al 2001) and will be used for the paediatric cohort.

The PedsQL 4.0 Generic Core Scales are multidimensional child self-reported and parent proxy-reported scales to assess HRQoL. PedsQL is a brief standardised paediatric HRQoL scale with good reliability and validity, which includes both generic and disease-specific modules. It consists of a 23-item core measure of global HRQoL that has 4 subscales: physical functioning, emotional functioning, social functioning, and school functioning.

The PedsQL Core version 4 has been developed in age-specific versions. In this study, the self-reported versions are for subjects aged 5 to 7 years, 8 to 12 years, and 13 to 17 years. In addition, the corresponding parent-reported versions will also be included. For subjects 3 to 4 years of age, only the parent-reported version will be included. Acute versions of the PedsQL questionnaires (7-day recall period) will be used in this study. The questionnaire takes approximately 5 to 10 minutes to complete.

8.1.3.2.2 EORTC QLQ-C30 and PlexiQoL (adult cohort)

For the adult cohort, the validated measures EORTC QLQ-C30 (Aaronson et al 1993) and PlexiQoL (Heaney et al 2019) will be used for assessments of HRQoL.

The EORTC QLQ-C30 was developed by the EORTC Quality of Life Group in 1993. It consists of 30 items and measures cancer patients' functioning (HRQoL) and symptoms for all cancer types (Aaronson et al 1993). Questions can be grouped into 5 multi-item functional scales (physical, role, emotional, cognitive, and social); 3 multi-item symptom scales (fatigue, pain, and nausea and vomiting); a 2-item global HRQoL scale; 5-single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea) and 1 item on the financial impact of the disease.

The PlexiQoL was developed through funding by The Neurofibromatosis Therapeutic Acceleration Program. It may be considered ancillary to the EORTC QLQ-C30. The impacts captured by this instrument, including shame/discomfort/embarrassment, negative body image, and impact on role, are not captured by the EORTC QLQ-C30. The European Medicines Agency issued a letter of support (January 2018) for consideration of the PlexiQoL for use in clinical studies (European Medicines Agency 2018).

8.1.3.3 Physical functioning

PROMIS is a set of person-centred measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions (PROMIS website).

The PROMIS Physical Functioning Scales assess the domains of Mobility and Upper Extremity Function and include mobility items such as "I can walk upstairs without holding on to anything" and upper extremity items such as "I can button my shirt or pants." Parent proxy items are parallel to child items. PROMIS paediatric 8-item short forms show good psychometric characteristics after large-scale testing (DeWitt et al 2011). The paediatric parent proxy physical functioning scales also can be used for children ages 5 to 7 years (Varni et al 2014).

Self-reported short forms will be administered to children from 8 to 17 years of age. Parallel parent proxy forms will be administered for children aged from 5 to 17 years. The short forms consists of 8 items using a 5-point Likert scale format (i.e. 1=unable to do, 5=can do without any difficulty). Raw scores are converted to a T–score, which is based on reference data from the US general population, where mean=50, standard deviation (SD)=10. The 2 forms take approximately 2 to 3 minutes to complete.

In the adult cohort, a separate newly developed Physical Function Short Form 8c 7-day scale will be used.

8.1.3.4 Patient's global impression of symptom severity

The PGIS instrument is a single-item scale that evaluates the patient's symptom severity (separate single items for tumour pain, overall pain and tumour-related problems) at different points in time. Global impression of symptom severity will be measured by asking the subject or parent to best describe how his/her symptoms are on a 6-point scale (0=no symptoms, 1=very mild, 2=mild, 3=moderate, 4=severe, 5=very severe).

The PGIS instrument will be parent-reported for children aged up to 17 years and self-reported for children aged 8 to 17 years and adults.

8.1.3.5 Patient's global impression of change

The PGIC instrument is a single-item scale that evaluates the subject's perspective of changes in their tumour pain, overall pain and tumour-related problems. It has been used in several research studies on chronic pain in adults and more recently children (Arnold et al 2011; Mohammad et al 2014), and has been recommended by the IMMPACT for clinical studies involving chronic pain (Dworkin et al 2005; McGrath et al 2008).

An adapted version of the PGIC instrument will be used in this study at all visits except baseline (it should not be given pre-study because it assesses the perceived change from baseline). A parallel parent proxy form will also be used. On the adapted PGIC, subjects (and their parents separately) will give their overall impression of change of the child's: 1) tumour pain, 2) overall pain, 3) tumour-related problems from before initiation of selumetinib to the current evaluation point.

PGIC will be parent-reported for children aged up to 17 years and self-reported for children aged 8 to 17 years and adults.

8.1.3.6 Administration of COAs

Baseline eCOAs should be completed at the site on Cycle 1 Day 1 before dosing using an eCOA site tablet. Thereafter, subjects should complete the eCOAs at the site at scheduled visits. A web-based system will be used if the device is not available.

All assessments should be completed according to the following parameters:

- Without assistance from site staff or anyone else and according to the study SoA. However, if the subject has difficulties reading, the site staff can read the instructions to the subject.
- Before any other study procedures are conducted at a given visit
- Before being seen by a study nurse or physician

Each study center must allocate the responsibility for the administration of the COAs to a specific individual (e.g., a research nurse or study coordinator) and, if possible, assign a backup person to cover if that individual is absent.

The investigator will arrange for relevant training in the set-up of the site tablet and train subjects in how to respond to the eCOAs. The significance and relevance of the COA data should be explained carefully to subjects so that they are motivated to respond.

The following guidelines should be followed:

- The following order for completion should be ensured (and the eCOA tablet should be programmed accordingly):
    - Pediatric cohort: FLACC or Faces Pain Scale (depending on age), PII, PROMIS Mobility, PROMIS Upper Extremity, PedsQL, PGIS, PGIC
    - Adult cohort: NRS-11, PII, PROMIS Physical Function, EORTC-QLQ-C30, PlexiQoL, PGIS, PGIC
- eCOA completion must be done by the subject in private and site staff should ensure that subjects have a quiet place to complete the assessments.
- Throughout the study, subjects will continue filling in the same age-specific versions of the instruments as they completed at baseline.
- In the adult cohort, responsible physician will select the target tumor for which subjects will assess the pain intensity. The target tumor will be selected from a prespecified list of body locations on the eCOA tablet before subjects start doing the assessments.
- The research nurse or appointed site staff must explain to subjects the value and relevance of study participation and inform them that these questions are being asked to find out, directly from them, how they feel. The research nurse or appointed site staff should also stress that the information is confidential. Therefore, if the subjects have any medical problems, they should discuss them with the doctor or research nurse separately from the eCOA assessment.
- The research nurse or appointed site staff must train the subject on how to use the eCOA device, using the materials and training provided by the eCOA vendor.
- The research nurse or appointed site staff should remind subjects that there are no right or wrong answers.
- The research nurse or appointed site staff must avoid clarifying items to avoid bias.
- The adult subject must not receive help from relatives, friends, or clinic staff to respond to the eCOAs. However, site staff is allowed to read instructions to subject if subject have difficulties reading.

  The research nurse or appointed site staff must monitor compliance to ensure all data is captured.

8.2 Safety assessments

Planned time points for all safety assessments are provided in Table 1. Notably, clinical chemistry, haematology, urinalysis, physical examination, vital signs, height and weight, ECG, echocardiogram, ophthalmologic assessment, Tanner stages and performance status will be assessed at screening, at the end of each cycle up to the end of Cycle 4, every 2 cycles up to the end of Cycle 12, every 4 cycles up to the end of Cycle 24, and every 6 cycles thereafter, as long as the subject remains on study treatment. Pregnancy tests will be performed at the end of each cycle. An x-ray will be performed at screening and at other visits/cycles, if clinically indicated. Safety assessments will also be performed at other visits during Cycles 0 and 1, as detailed in Table 1.

8.2.1 Clinical safety laboratory assessments

See Table 10 for the list of clinical safety laboratory tests to be performed and Table 1 for their timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and Table 1. The blood sample for clinical chemistry should be collected under fasting status. The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF.

Clinical chemistry, haematology and urinalysis assessments will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site.

Table 10 Laboratory safety variables

Haematology/Haemostasis (whole blood)	**Clinical chemistry (serum or plasma)**
B – Erythrocyte count	S/P – Albumin
B – Haemoglobin	S/P – Alkaline phosphatase
B – Platelet count	S/P – Alanine aminotransferase
B – Leukocyte count	S/P – Aspartate aminotransferase
B – Leukocyte differential count (absolute count)	S/P – Total calcium
B – Neutrophil count	S/P – Creatinine
B – Eosinophil count	S/P – Gamma-glutamyl transferase
B – Basophil count	S/P – Magnesium
B – Lymphocyte count	S/P – Phosphate
B – Monocyte count	S/P – Potassium
	S/P – Sodium
Urinalysis (dipstick)	S/P – Total protein
U – Glucose	S/P – Total bilirubin
U – Protein/albumin	S/P – Urea nitrogen[a]
U – Haemoglobin/erythrocytes/blood/ Leucocytes	S/P – Uric acid
	S/P – Creatine kinase[b] S/P – Amylase
	S/P – Troponin (isoform per site norm)[c]

B=blood; CK=creatine kinase; LLN=lower limit of detection; LVEF=left ventricular ejection fraction; P=plasma; S=serum; U=urine.

[a] Urea or blood urea nitrogen based on local site practice.

[b] CK to be assessed at screening and if clinically indicated (e.g. muscle symptoms).

[c] Troponin (isoform per site norm), should be assessed at screening, and performed when there is a significant drop in LVEF (of ≥10 percentage points relative to baseline and to an absolute LVEF below the institution's LLN on study treatment) or for any cardiorespiratory events with no obvious diagnosis. If troponin assessments are not available, per local practice, CK-MB isoform should be assessed. Subjects should be managed according to the algorithm provided in Appendix E.

Clinical chemistry, haematology and urinalysis testing will be repeated as clinically indicated as part of the routine management of the subject on the occurrence of AEs.

Urine microscopy will be assessed if other urinalysis measurements are abnormal or if clinically indicated.

If unexplained muscle weakness or myalgia (muscle pain) occurs, the subject should have a neuromuscular examination, urine analysis and CK measurement performed (with an additional CK-MM isoform measurement where possible) and be managed according to local practice.

All subjects with an AST, ALT or bilirubin value ≥1.5×ULN at time of the last dose of selumetinib should have a further liver chemistry profile (AST, ALT, bilirubin and alkaline phosphatase [ALP]) performed 30 days (±7 days) after permanent discontinuation of selumetinib.

N.B. In the case of a subject showing an AST **or** ALT ≥3×ULN together with total bilirubin ≥2×ULN, please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law' (HL), for further instructions.

8.2.1.1 Pregnancy test

Pregnancy tests (blood or urine tests are acceptable based on the site's standard clinical practice) should be performed for women of childbearing potential only (see Section 5.1). Pregnancy testing will be performed at screening, Cycle 0 Day 1 and at the end of each cycle in women of childbearing potential only (see Section 5.1 for details) and more frequently, if clinically indicated as outlined in Table 1.

8.2.2 Physical examinations

A complete physical examination will be performed and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities) and neurological systems.

Physical examination will be performed at the times specified in Table 1. Investigators should pay special attention to clinical signs related to previous serious illnesses. New or worsening abnormalities may qualify as AEs (see Section 8.3.7).

8.2.3 Vital signs

Axillary temperature, pulse rate, oxygen saturation by pulse oximetry, respiratory rate, and BP will be assessed in accordance with Table 1 and additionally at the discretion of the investigator if clinically indicated.

Vital signs will be taken prior to blood collection.

Blood pressure and pulse measurements will be assessed in a sitting position and preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g. television, cell phones). Manual techniques will be used only if automated devices are not available.

8.2.4 Height and weight

Height and weight will be measured at the times outlined in Table 1. The subject's height will be recorded in centimetres (cm) and weight will be recorded in kilograms (kg). Height and weight measurements will be performed in light clothing and with shoes off.

For paediatric subjects:

Collect all available documented previous height and weight measurements and growth curves if available at screening.

Height: The subjects should take off shoes and socks, and heels should be placed against a wall with ankles together. Height should be measured in a standing position with a stadiometer. Height measurements should be taken at approximately the same time of day for each visit, when possible. The height should be plotted on a standardised growth chart. In subjects with known leg length discrepancy due to limb hypertrophy, height should be measured with the subject bearing weight on the limb without hypertrophy.

8.2.5 Electrocardiograms

Single 12-lead ECGs will be obtained locally at the site. ECGs will be evaluated at the times outlined in Table 1 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and corrected QT intervals. Subjects should be supine and at rest 5 minutes prior to recording the ECG. RR interval and QTcF will be calculated by AstraZeneca from the data provided.

The investigator should review the paper copy of the ECGs on each study day and may refer to a local cardiologist if appropriate.

If an abnormal ECG finding at the screening assessment is considered to be clinically significant by the investigator, it should be reported as a concurrent condition. During the study, clinically significant abnormal ECG findings not present at screening should be reported as an AE. If present, the clinical signs and symptoms associated with the abnormal finding should be reported as an AE, with the ECG abnormality given as explanatory information.

Single ECGs should be performed at the time of significant LVEF drop (Section 8.2.6) and on occurrence of any cardiorespiratory AEs with no obvious diagnosis. For subjects with new or worsening respiratory symptoms (such as dyspnoea or cough), an ECG is recommended, and additionally at the discretion of the investigator if clinically indicated.

8.2.6 Echocardiogram

Echocardiograms will be performed and analysed locally at the site. Echocardiograms will be evaluated the times outlined in Table 1. A further assessment should be performed as part of the assessment package for any cardiorespiratory AE with no obvious diagnosis (obvious causes will be managed in accordance with local clinical practice) and additionally at the discretion of the investigator if clinically indicated.

Medical management of the event should follow local clinical practice. Selumetinib interruption/modification should be considered until resolution of the event or until return to baseline, for which discussion between the sponsor and study investigator is encouraged. Subjects who have a drop in LVEF of ≥10 percentage points from baseline and to below the LLN at the time of selumetinib discontinuation should, where possible, have a follow-up echocardiogram, ECG, vital signs and weight performed after 30 days to evaluate the potential for reversibility.

The subject should be examined using the same machine and operator throughout the study wherever possible.

LVEF, end diastolic and end systolic left ventricular volumes should be recorded at each echocardiogram assessment. An echocardiogram will also be carried out if a subject develops signs and/or symptoms suggestive of deterioration in left ventricular function/cardiac event.

Subjects experiencing an asymptomatic but clinically significant drop in LVEF (decrease by ≥10 percentage points relative to baseline and below the LLN) should be managed according to the algorithm provided in Appendix E.

Concomitant cardiac symptoms should be reported as AEs/SAEs accordingly. Cardiac failure should be treated and followed according to local medical practice.

8.2.7 Ophthalmologic examination

An ophthalmologic examination (best corrected visual acuity, IOP and slit-lamp fundoscopy) will be evaluated at the times outlined in Table 1, and as clinically indicated whilst the subject is on study treatment.

If a subject experiences symptoms of visual disturbance (including blurring of vision), a complete ophthalmological examination, including a slit-lamp examination, must be performed. If an abnormality is detected, fundus photography and an optical coherence tomography scan can also be performed where required. AEs are to be managed according to Appendix E.

If a retinal abnormality prior to or at time of selumetinib discontinuation is observed, a repeat ophthalmological examination is to be performed 30 days after discontinuation of selumetinib in order to document reversibility.

8.2.8 Performance status

Performance status will be measured as indicated in Table 1. Karnofsky scoring will be used for subjects aged >16 years, and Lansky scoring will be used for subjects aged ≤16 years. These scales are described in more detail in Appendix G.

8.2.9 X-ray in paediatric subjects

Yearly growth assessments require integration of information including height measurements, puberty staging (Tanner staging), and bone age if clinically indicated, which should be plotted onto growth charts. Children with impaired growth velocity should be referred to a paediatric endocrinologist as clinically indicated for evaluation, and should be followed until they reach final adult height.

An X-ray of the hand and wrist will be performed at screening and at other visits/cycles if clinically indicated, as specified in Table 1, to monitor growth plates and the potential risk of physeal dysplasia.

The investigator should regularly look for signs of physeal dysplasia (e.g. joint pain and fatigue after exercising, abnormal gait, and spine irregularities) in the paediatric population. Children who show signs of physeal dysplasia at the time of selumetinib discontinuation should have a follow-up assessment after 30 days to evaluate the potential for reversibility.

8.2.10 Tanner stages in paediatric subjects

For paediatric subjects, Tanner stages (sexual maturity rating according to the local site) will be assessed at the times outlined in Table 1.

8.3 Collection of adverse events and Serious adverse events

The principal investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legal guardian).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs, see Section 8.3.3.

8.3.1 Method of detecting adverse events and serious adverse events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject/care provider is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting adverse event and serious adverse event information

All AEs, including SAEs, will be collected from the time the ICF (subject or parent/legal guardian) is signed, throughout the treatment period and up to the 30-day safety follow-up visit (30 days after the last dose of study treatment).

From the 30-day safety follow-up visit until the end of the long-term post-treatment safety follow-up visit:

1 All SAEs regardless of causality will be collected.

2 Only AEs considered causally related to selumetinib will be collected.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix B and Sections 8.3.5 and 8.4.1.

8.3.3 Follow-up of adverse events and serious adverse events

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs/nonserious AEs will be followed until resolution, stabilisation, the event is otherwise explained, or the subject is lost to follow-up

Any AEs that are unresolved at the subject's last visit in the study will be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The requirement to follow-up AEs is not intended to delay database lock or production of the CSR. These activities should proceed as planned with ongoing AEs if necessary.

Any follow-up information of ongoing SAEs after database lock will be reported to AstraZeneca, and the outcome of the SAE will be updated, if appropriate.

8.3.4 Adverse event data collection

The following variables will be collected for each AE;

- AE (verbatim);
- The date when the AE started and stopped;
- CTCAE grade/max CTCAE grade/changes in CTCAE grade;
- Whether the AE is serious or not;
- Investigator causality rating against the IP (yes or no);
- Action taken with regard to IP;
- AE caused subject's withdrawal from study (yes or no);
- AE required treatment (yes or no);
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE;
- Date investigator became aware of serious AE;
- AE is serious due to;
- Date of hospitalisation;
- Date of discharge;
- Probable cause of death;
- Date of death;
- Autopsy performed;
- Causality assessment in relation to study procedure(s);
- Causality assessment to other medication;
- Description of AE.

8.3.5 Causality collection

The investigator will assess the causal relationship between the IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IP?'

For SAEs, a causal relationship will also be assessed for other medications and study procedures.

A guide to the interpretation of the causality question is found in Appendix B.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or his/her parent(s)/legal guardian or reported in response to the open question from the study site staff: **Have you/the child had any health problems since the previous visit/you were last asked?**, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the CSP-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in CSP-mandated laboratory values or vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study treatment, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (e.g. anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (see Sections 8.3.9 and 8.3.10).

8.3.8 Hy's law

Clinical safety laboratory tests will be performed for all subjects at screening and regularly throughout the study as indicated in Table 1.

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN may need to

be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

8.3.9 Disease under study

Symptoms of disease under study are those which might be expected to occur as a direct result of NF1 and inoperable PN. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP. Symptoms of disease under study such as pain will be recorded as efficacy measurements and collected during the study in the relevant eCRF.

8.3.10 Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing NF1-related PN under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AEs during the study.

8.3.11 Adverse events of special interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of selumetinib safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESI should be recorded in the eCRF as soon as possible, and preferably within 24 hours of occurrence. Serious AESIs will be recorded and reported as per Section 8.4.1. Adverse events of special interest based on examinations and tests should be reported in accordance with Section 8.3.7. Adverse events of special interest are shown in Table 11.

Table 11 Adverse Events of Special Interest

AESI	MedDRA Preferred Terms (PT) Defining the AESIs
Ocular toxicity	Chorioretinopathy (central serous retinopathy [CSR]); Retinal detachment; Retinal tear; Vision blurred; Visual impairment; Vitreous floaters; Photopsia; Eye disorder; Photophobia; Retinal vein occlusion (RVO); Detachment of retinal pigment epithelium (Retinal pigment epithelial detachment [RPED]).
Hepatotoxicity	Drug-induced liver injury; ALT increased; AST increased.
Muscular toxicity	Blood creatine phosphokinase increased; Musculoskeletal pain; Muscular weakness; Myalgia; Rhabdomyolysis; Myoglobin blood increased; Myoglobin urine present; Acute kidney injury; Myopathy.
Cardiac toxicity	Ejection fraction decreased; Oedema peripheral; Peripheral swelling; Oedema; Left ventricular dysfunction; Ventricular dysfunction.

AESI	MedDRA Preferred Terms (PT) Defining the AESIs
For Paediatric population only	
Physeal dysplasia	Metaphyseal dysplasia, Multiple epiphyseal dysplasia, Arthralgia, Joint stiffness, Joint hyperextension, Gait disturbance, Short stature.
Choking on the capsule	Choking, Retching.

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate AstraZeneca representatives within **1 day** (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the investigator or other study site staff must report an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the investigator/study site staff how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca IP.

For further guidance on the definition of an SAE, see Appendix B of the CSP.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study subject has received any IP. If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, foetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Male subjects with reproductive potential must be surgically sterile or using an acceptable method of contraception (defined as barrier methods in conjunction with spermicides) for the duration of the study (from the time they sign consent) and for at least 12 weeks after the last dose of study treatment to prevent pregnancy in a partner. Male subjects with reproductive potential must not donate or bank sperm during this same time period.

Pregnancy of the subject's partners will not be considered an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented in the pregnancy report form for conceptions occurring from the date of the first administration of IP until at least 12 weeks after the last dose of IP. Consent from the partner must be obtained before the pregnancy report form is completed.

8.4.3 Overdose

For this study, any dose of selumetinib greater than the assigned dosage will be considered an overdose.

Overdose should be followed up and treated with appropriate supportive care until recovery.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose of an AstraZeneca IP occurs in the course of the study, then the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medication error

If a medication error occurs during the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (i.e. immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of investigational product-related toxicities

Recommendations for the management or investigation of specific AEs is provided in Appendix E.

Dose modification guidance is included in Section 6.6.

8.5 Pharmacokinetics

A pharmacokinetic evaluation will be performed after the first dose of selumetinib, and at steady state in all consenting adult and paediatric subjects. The PK blood sampling time points are shown in Table 12 (single dose) and Table 13 (multiple doses).

Subjects are to be hospitalised for intensive PK sampling during the single dose period (from Cycle 0 Day -1 to Cycle 0 Day 2) and also on Cycle 1 Day 8.

Table 12 Pharmacokinetic sampling schedule (single dose)

Cycle 0	Day	Pre-dose[a]	30 min[b]	1 hr[c]	1.5 hr[c]	3 hr[c]	6 hr[c]	8 hr[c]	12 hr[c]	24 hr[c]	30 hr[c]
	1	x	x	x	x	x	x	x	x	x	x

hr=hour; min=minute.
[a] Within 10 minutes prior to dosing.
[b] Time allowance: ±5 minutes.
[c] Time allowance: ±10 minutes.

Table 13 Pharmacokinetic sampling schedule (multiple doses)

Cycle 1	Day	Pre-dose[a]	30 min[b]	1.5 hr[c]	3 hr[c]	6 hr[c]	12 hr[c]
	8	x	x	x	x	x	x

hr=hour; min=minute.
[a] Within 10 minutes prior to dosing.
[b] Time allowance: ±5 minutes.
[c] Time allowance: ±10 minutes.

Whole blood samples at each time point will be collected for measurement of the plasma concentration of selumetinib and its metabolite N-desmethyl selumetinib following a single dose (Table 12) and multiple doses (Table 13) as specified in Table 1. PK parameters assessed may include, but are not limited to the following after a single dose:

- AUC.
- Area under the concentration-time curve from zero to 12 hours (AUC_{0-12}).

- Area under the concentration-time curve from zero to the last measurable concentration (AUC_{0-t}).
- C_{max}.
- Time to maximum plasma concentration (t_{max})
- Terminal half-life ($t_{1/2}$).

PK parameters assessed may also include, but are not limited to the following after multiple doses:

- Area under the concentration-time curve from zero to 12 hours at steady state ($AUC_{0-12,ss}$).
- Maximum steady-state plasma concentration ($C_{max,ss}$).
- Accumulation ratio (Rac; AUC and $C_{max)}$.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. Instructions for the collection and handling of biological samples will be provided by the sponsor or analytical test site. The actual date and time (24-hour clock time) of each sample will be recorded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

Analyses of PK and safety may also be performed several times prior to completion of the study in order to facilitate health authority engagement.

8.5.1 Determination of drug concentration

Samples for determination of selumetinib and N-desmethyl selumetinib concentration in plasma will be analysed by Covance on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a Bioanalytical Report.

Selectivity (in a patient population) analysis, if any, may be performed alongside the bioanalysis using PK pre-dose samples. The results from the evaluation will not be reported in the CSR, but separately in a Bioanalytical Report.

8.5.2 Storage and destruction of pharmacokinetic samples

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Pharmacokinetic samples will be disposed of after finalisation of the Bioanalytical Report.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Health economics or medical resource utilisation and health economics

Health economics/medical resource utilisation and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal statistical hypotheses will be tested.

9.2 Sample size determination

The primary objectives are to evaluate the safety, tolerability and PK of selumetinib. Approximately 16 paediatric and 16 adult subjects with NF1 and inoperable PN will be enrolled in the study to obtain adequate PK and safety data. Per the Chinese Phase 1 PK guideline, at least 8 to 12 subjects per cohort are required. To allow for dropouts and nonevaluable cases, 16 subjects in each cohort will be enrolled. There must be a minimum of 6 subjects each in the 3 to 11 and 12 to 17 year age groups at the time of enrolment.

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Safety analysis set	The safety analysis set consists of all subjects who receive at least 1 dose of selumetinib.
Pharmacokinetic analysis set	All subjects who receive at least 1 dose of selumetinib and have at least 1 post-dose evaluable concentration-time data point.

9.4 Outcome measures for analyses

9.4.1 Calculation or derivation of pharmacokinetic variables

PK analysis of the plasma concentration data for selumetinib and N-desmethyl selumetinib will be performed by AstraZeneca or a Contract Research Organisation on behalf of AstraZeneca. The actual sampling times will be used in the parameter calculations and PK parameters will be derived using standard noncompartmental methods.

Where possible, the following PK parameters will be determined with plasma concentration data of selumetinib and N-desmethyl selumetinib: AUC, AUC_{0-12}, AUC_{0-t}, C_{max}, t_{max}, and $t_{1/2}$ after a single dose, and $AUC_{0-12,ss,}$ $C_{max,ss}$, and Rac (for AUC and C_{max}) after multiple doses.

The C_{max}, $C_{max,ss}$ and t_{max} will be determined by inspection of the concentration-time profiles. The $t_{1/2}$ will be calculated as $\ln 2/\lambda z$, where λz will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data. The AUC_{0-12}, $AUC_{0-12,ss}$, and AUC_{0-t} will be calculated using the linear/log trapezoidal rule (i.e. "linear-up-log-down": the linear trapezoidal rule is used any time that the concentration data are increasing, and the logarithmic trapezoidal rule is used any time that the concentration data are decreasing). Where appropriate, the AUC_{0-t} will be extrapolated to infinity using λz to obtain AUC. The Rac (AUC) and Rac (C_{max}) will be calculated as the ratio of the $AUC_{0-12,ss}$ or $C_{max,ss}$ following multiple dosing by the AUC_{0-12} or C_{max} following the first dose, respectively.

9.4.2 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, clinical safety laboratory assessments, physical examination, vital signs, weight/height, ECG, echocardiogram, performance status, and ophthalmologic assessment for both paediatric and adult cohorts. For the paediatric cohort only, bone growth assessments and Tanner stages will also be collected.

9.4.3 Calculation or derivation of efficacy variables

9.4.3.1 Tumour response

9.4.3.1.1 Objective response rate

Objective response rate (ORR) is defined as the proportion of subjects who have a CR or confirmed PR (defined as target PN volume decrease ≥20% compared to baseline and confirmed by a consecutive scan within 3 to 6 months after first response), as determined by independent central review and investigator per REiNS criteria.

Best overall response (BOR) is defined as the best response recorded from the start of the treatment until progression or the last evaluable MRI assessment in the absence of progression.

9.4.3.1.2 Duration of response

Duration of response (DoR) is defined as the time from the date of the first documented response (which is subsequently confirmed) until the date of documented progression or death in the absence of disease progression, as determined by independent central review and investigator per REiNS criteria.

9.4.3.1.3 Progression free survival

Progression-free disease (PFS) is defined as the time from the date of first dose until progression per REiNS criteria as assessed by independent central review and investigator, or death due to any cause.

9.4.3.1.4 Time to progression

Time to progression (TTP) is defined as the time from the date of first dose until progression per REiNS criteria as assessed by independent central review and investigator.

9.4.3.1.5 Time to response

Time to response (TTR) is defined as the time from the date of first dose until the date of the first documented response (which should be subsequently confirmed if it's a partial response), as determined by independent central review and investigator per REiNS criteria.

9.4.3.2 Disfigurement

Detailed recommendations for photography techniques are provided in the photography manual.

9.4.4 Calculation or derivation of clinical outcome assessment variables

9.4.4.1 Pain

9.4.4.1.1 FLACC pain scale (3 years)

The FLACC pain scale will be assessed as scheduled in Table 1. Change from baseline will be derived for each visit.

9.4.4.1.2 Faces pain scale – revised (4 to 17 years)

The Faces pain scale will be assessed as scheduled in Table 1. Change from baseline will be derived for each visit.

9.4.4.1.3 NRS-11 (adult cohort)

The NRS-11 consists of 4 questions scored on an 11-point scale 0=no pain to 10=worst pain you can imagine. The primary outcome for the self-reported NRS-11 will be the rating of one specific tumour pain (e.g. the "target tumour"). This pain rating will be the physician-selected target tumour.

9.4.4.1.4 Pain interference index

The PII is a 6-item scale that assesses the extent to which pain has interfered with an individual's daily activities in the past 7 days. Items are rated on a 7-point Likert scale (0=not at all to 6=completely), and the total scale is the mean of the completed items. The total scale will be computed if at least 50% of items are answered (e.g. 4 out of 6).

9.4.4.2 Health-related quality of life

9.4.4.2.1 PedsQL (paediatric cohort)

The generic PedsQL consists of 23 questions and yields a total score. The 4 subscales are: 1) physical functioning (8 items), 2) emotional functioning (5 items), 3) social functioning (5 items), and 4) school functioning (5 items). Each item is scored on a 5-point Likert scale (0=never a problem; 1=almost never a problem; 2=sometimes a problem; 3=often a problem; 4=almost always a problem). For self-reported and parent/guardian reported separately, items are reverse-scored and linearly transformed to a 0 to 100 scale (0=100, 1=75, 2=50, 3=25, 4=0), so that higher scores indicate better HRQoL. Scale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). A Total Scale Score will also be derived as the sum of all the items divided by the number of items answered on all the scales. If more than 50% of the items in the scale are missing, the scale score is not computed (Nutakki et al 2018). In addition, scale scores will be calculated using the raw item scores (without the linear transformation, but still reversed).

The primary outcomes for HRQoL will be the Total Scale Score of the self-reported PedsQL for children ≥5 years of age and the Total Scale Score of the parent PedsQL administered to parents of children 3 to 4 years of age.

Secondary outcomes for HRQoL will be the mean scores of the 4 domains (physical, emotional, social, and school) of the self-reported scale completed by children >5 years of age and the 4 domain mean scores from the parent-reported scale given to parents of children 3 to 4 years of age.

9.4.4.2.2 EORTC QLQ-C30 (adult cohort)

The EORTC QLQ-C30 consists of 30 questions that can be combined to produce 5 functional scales (physical, role, emotional, cognitive, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), 5 individual items (dyspnoea, insomnia, appetite loss, constipation, and diarrhoea), and a global measure of health status. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual. An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales/symptom items, each of the functional scales, and the global health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent greater symptom severity.

9.4.4.2.3 PlexiQoL (adult cohort)

The PlexiQoL consists of several questions that are each answered as "true" if the statement applies or "false" if the statement does not apply. The time frame for the assessment is "at the moment." These statements assess whether the subject avoids crowds, are unable to join activities with family and friends, etc.

9.4.4.3 Physical functioning

Physical functioning will be assessed as scheduled in Table 1 using the PROMIS measures for mobility and upper extremity. Both raw and T-scores will be analysed separately. Higher scores indicate better physical functioning.

9.5 Statistical analyses

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan (SAP) will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the CSR.

Same DCOs would be applied for both analysis of pediatric cohort and adult cohort. Primary DCO in this study will take place when the last subject dosed has had the chance to complete their visit at the end of cycle 10. Final DCO will occur when the last subject dosed has had the chance to complete their visit at the end of cycle 24. In addition, an interim analysis will be conducted when last subject dosed has had the chance to complete their visit at the end of cycle 4 to assess PK, safety, tolerability and efficacy in Chinese subjects with NF1 and inoperable PN.

Data from the paediatric and adult cohorts will be analysed separately. In general, baseline is defined as the last assessment before the first dose of selumetinib. Demographic data and baseline subject characteristics will be analysed for the safety analysis set. PK will be analysed based on the PK analysis set. Efficacy, clinical outcome assessment, exposure and safety data will be analysed based on the safety analysis set.

9.5.1 Pharmacokinetic analyses

Plasma concentrations will be listed and summarised by cohort, analyte, dose level (if applicable), and nominal sample time using the following summary statistics:

- The G_{mean} (calculated as exp [μ], where μ is the mean of the data on a logarithmic scale).
- Geometric coefficient of variation (GCV) calculated as $100\sqrt{(\exp(s^2)-1)}$, where s is the SD of the data on a log scale.
- G_{mean}±SD (calculated as exp[μ±s]).
- Arithmetic mean calculated using untransformed data.
- SD calculated using untransformed data.
- Coefficient of variation (CV; % CV calculated using untransformed data).
- Median.
- Minimum.
- Maximum.
- Number of observations.
- Number of observations below the lower limit of quantification (LLOQ; n below LLOQ).

The derived PK parameters except t_{max} will be summarised by cohort, analyte, and dose level (if applicable) using the following summary statistics:

- G_{mean} (calculated as exp [μ], where μ is the mean of the data on a logarithmic scale).
- GCV (calculated as $100\sqrt{(\exp(s^2)-1)}$, where s is the SD of the data on a log scale).
- G_{mean}±SD.
- Arithmetic mean calculated using untransformed data.
- SD calculated using untransformed data.
- CV (% CV, calculated using untransformed data).
- Median.
- Minimum.
- Maximum.

- Number of observations.

The following summary statistics will be presented for single dose and/or steady state t_{max}:

- Median.
- Minimum.
- Maximum.
- Number of observations.

Dose/BSA-normalised PK parameters for selumetinib and its metabolite (N-desmethyl selumetinib) will be summarised as appropriate.

The PK data or dose/BSA-normalised PK parameters for selumetinib and its metabolite (N-desmethyl selumetinib) after a single dose and multiple doses, respectively, will also be displayed graphically. Displays may include plasma concentration subject profiles (on the linear and log-scale) versus time and G_{mean} concentration (on the linear and log-scale) versus time. Scatter plots of PK parameters may also be presented as appropriate.

9.5.2 Safety analyses

Safety analyses will be performed using the safety analysis set.

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities that will have been released for use by AstraZeneca/designee.

Safety data will be presented by using descriptive statistics and by cohort unless otherwise specified.

AEs will be presented for each cohort by System Organ Class and/or Preferred Term covering the number and percentage of subjects reporting at least 1 event and the number of events where appropriate.

AEs occurring prior to the start of IP and treatment-emergent AEs will be presented separately.

An overview of AEs will be presented for each cohort. The number and percentage of subjects with any AE, AEs with outcome of death, SAEs, AEs leading to discontinuation of IP, AEs leading to IP dose interruptions, AEs leading to IP dose reduction and AEs leading to

withdrawal from study, as well as the number of individual occurrences in those categories, will be presented.

Separate AE tables will be provided taking into consideration causal relationship as assessed by the investigator, CTCAE grading, seriousness, death and events leading to discontinuation of IP as well as other actions taken related to IP, AEs of special interest, and other significant AEs.

An additional table will present the number and percentage of subjects with the most common AEs (frequency of >10%).

Key subject information will be presented for subjects with AEs with an outcome of death, SAEs, and AEs leading to discontinuation of IP.

An AE listing for the safety analysis set will cover details for each individual AE.

Full details of AE analyses will be provided in the SAP.

The following events are considered to be treatment-emergent:

- AEs with an onset date on or after the first dose of IP and within 30 days after the last dose of IP.
- Worsening of pre-existing events on or after the first dose of IP and within 30 days after last dose of IP.

Laboratory data (haematology, clinical chemistry and quantitative urinalysis) will be summarised using descriptive statistics over time in terms of absolute values and changes from baseline. Shift tables showing CTCAE grade changes from baseline on treatment will be produced by laboratory parameter for haematology and clinical chemistry.

All vital signs and height, weight and BSA will be summarised using descriptive statistics over time in terms of absolute values and change from baseline.

Other safety assessments (pregnancy test, physical examination, ECG, echocardiogram, ophthalmologic examination, performance status, bone growth monitoring and Tanner staging) will be listed and summarised where appropriate. Box plots of laboratory and vital signs data may be provided if needed.

9.5.3 Efficacy analyses

Efficacy analyses will be performed using the safety analysis set.

Efficacy endpoints (ORR, DoR, PFS, TTR and TTP) based on independent central review and investigator assessments will be analysed separately. The discordance between the independent central review and the investigator will be provided.

ORR will be presented with corresponding 2-sided exact 95% CI based on the Clopper-Pearson method (Clopper and Pearson 1934). Descriptive statistics will be provided for BOR. Change in PN growth will be evaluated descriptively by summaries of percentage and absolute change in PN volume from baseline. The best percentage change from baseline will be summarised descriptively and presented graphically using waterfall plots. Spaghetti plots showing individual subject tumour volume and percentage change in tumour volume will also be produced.

Kaplan-Meier plots of DoR, PFS, TTR and TTP will be presented. The median DoR, PFS, TTR, TTP and 95% CI will be calculated using the Kaplan-Meier method.

For analysis of disfigurement, anonymised photographs of PN-related morbidity will be provided in the individual subject reviews, where appropriate.

9.5.4 Clinical outcome assessment analyses

All functional and clinical outcome assessment analyses will be performed on the safety analysis set unless otherwise noted. The analysis of the clinical outcome assessments and functional outcomes will be based on descriptive statistics.

For analysis of the clinical outcome assessments, the self-reported and parent/guardian-reported questionnaires will be analysed and presented separately.

9.5.4.1 Pain

9.5.4.1.1 FLACC pain scale (3 years)

Individual FLACC pain scale scores and change from baseline scores will be listed and plotted as appropriate.

9.5.4.1.2 Faces pain scale - revised (4 to 17 years)

Descriptive statistics for the Faces pain scale and change from baseline will be provided for each visit. A line graph with mean values/mean change from baseline values and corresponding 95% CI will be presented. Other analyses may be performed as appropriate. Further details will be provided in the SAP.

9.5.4.1.3 NRS-11 (adult cohort)

Descriptive statistics for the pain intensity scores and change from baseline will be provided for each visit. A line graph with mean values/mean change from baseline values and

corresponding 95% CI will be presented. Other analyses may be performed as appropriate. Further details will be provided in the SAP.

9.5.4.1.4 Pain interference index

Descriptive statistics for the PII score and change from baseline will be provided for each visit. A line graph with mean values/mean change from baseline values and corresponding 95% CI will be presented. Other analyses may be performed as appropriate. Further details will be provided in the SAP.

9.5.4.2 Health-related quality of life

9.5.4.2.1 PedsQL (paediatric cohort)

Descriptive statistics for the PedsQL scores (total score, and the 4 domain scores) and change from baseline in PedsQL scores (total score, and the 4 domain scores) will be provided for each visit. A line graph with mean values/mean change from baseline values and corresponding 95% CI will be presented. Other analyses may be performed as appropriate. Further details will be provided in the SAP.

9.5.4.2.2 EORTC QLQ-C30 (adult cohort)

Descriptive statistics of original and change from baseline values of each symptom scale/item, the global HRQoL score and each functional domain will be reported by visit. Graphical presentations may also be produced as appropriate. Further details will be provided in the SAP.

9.5.4.2.3 PlexiQoL (adult cohort)

Individual data will be listed. Other analyses may be performed as appropriate. Further details will be provided in the SAP.

9.5.4.3 Physical functioning

Descriptive statistics for the mobility and upper extremity scores (item scores, raw and T-scores for each domain) and change from baseline (item scores, raw and T-scores for each domain) will be provided for each visit. A line graph with mean values/mean change from baseline values and corresponding 95% CI will be presented. Other analyses may be performed as appropriate. Further details will be provided in the SAP.

9.5.4.4 Patient's global impression of symptom severity

Counts and percentages for each question at each visit will be presented.

9.5.4.5 Patient's global impression of change

Counts and percentages for each question at each visit will be presented.

9.6 Interim analyses

Same DCOs would be applied for both analysis of pediatric cohort and adult cohort. In addition, an interim analysis will be conducted when last subject dosed has had the chance to complete their visit at the end of cycle 4 to assess PK, safety, tolerability and efficacy in Chinese subjects with NF1 and inoperable PN.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines;
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- For all studies except those utilising medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB (or other supporting documents] and will notify the IRB/IEC, if appropriate according to local requirements.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her legal guardian will explain the nature of the study to the subject or his/her legal guardian and answer all questions regarding the study.

Subjects and/or their parents/legal guardian must be informed that participation is voluntary. Subjects or their legal guardian (when applicable per regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre. When applicable and per local regulations, assent will be provided by subjects.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

There is no uniform standard with regards to the age limit above which paediatric subjects' own informed consent is valid. Article 12 of the *General Principles of the Civil Law of China* states that a minor aged 10 years or less is a person without capacity of civil conduct, who

shall be represented in civil activities by his/her legal guardian. In China, subjects aged 10 years and above should, in most instances, be involved in informed consent and sign the ICF. It should be noted however that in cases involving special diseases, such as mental cognitive developmental disorders, whether to participate in and sign informed consent depends not only on the subject's age, but also on his/her ability to provide informed consent. Thus, in deciding whether a paediatric subject himself/herself should participate in or sign the informed consent, a sufficient basis should be proposed, and the Ethics Committee is to review and determine whether the target subject is qualified for informed consent.

If the Ethics Committee reviews and determines that a study needs the informed consent of the paediatric subjects, respecting the subject's own wishes is essential and, throughout the study, such wishes should be continuously paid attention to. If a paediatric subject does not consent to participate in a clinical study or decides to withdraw during a study, the subject's decision should prevail, even if the parents/legal guardians have previously agreed with the subject's participation or are willing to let subject continue the clinical study. When the subject expresses that he/she is unwilling to continue participating in the studies, investigators should carefully assess the situation and confirm that the decision was made by the subject out of his/her own accord.

Generally, paediatric drug clinical studies should not recruit a paediatric population requiring special care or supervision by a court/social welfare institution (except for drug clinical studies conducted exclusively for these groups), because these groups may not enjoy the full protection in terms of ethical considerations.

Oral informed consent is a method to inform paediatric subjects who are not qualified to sign an informed consent, which is favourable to the study compliance of subjects, but cannot be used to replace the signing of informed consent (when qualified to sign the informed consent).

For subjects who reach the age of legal consent during the clinical study, notification may be required and a new consent form may need to be signed by the subject.

Subjects and/or their parents/legal guardian must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject, parents or the subject's legal guardian.

If a subject's partner becomes pregnant during or within 12 weeks after the study, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Subjects" and provide information about the pregnancy accordingly.

Subjects who are rescreened are required to sign a new ICF.

If a subject and/or their parents/legal guardian withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples have already been analysed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the CSP and letters to investigators.

A 6 Dissemination of clinical study data

A description of this clinical study will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data quality assurance

All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and site closure

The sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, study subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant;
- are assessed as causally related to study treatment;

- are not considered to be consistent with continuation of the study.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of study follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and nonserious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definitions of serious adverse event

An SAE is an AE occurring during any study phase (i.e. run-in, treatment, washout and follow-up), that fulfils one or more of the following criteria:

- Results in death;
- Is immediately life-threatening;
- Requires in-subject hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important medical event that may jeopardise the subject or may require medical treatment to prevent one of the outcomes listed above.

AEs for malignant tumours reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a nonserious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as nonserious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e. it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g. Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

B 3 Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g. hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (e.g. bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardise the subject or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

Important medical events may include:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment;
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine;
- Intensive treatment in an emergency room or at home for allergic bronchospasm;

- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation;
- Development of drug dependency or drug abuse.

B 6 Intensity rating scale

The grading scales found in the revised NCI CTCAE version 5.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the following recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self care ADL. Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

  A semi-colon indicates ‘or’ within the description of the grade.

B 7 A guide to interpreting the causality question

When making an assessment of causality, consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognised feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca IP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred.

- Was identified and intercepted before the participant received the drug.
- Did not occur, but circumstances were recognised that could have led to an error.

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion;
- Dispensing error (e.g. medication prepared incorrectly, even if it was not actually given to the participant);
- Drug not administered as indicated, for example, wrong route or wrong site of administration;
- Drug not taken as indicated (e.g. tablet dissolved in water when it should be taken as a solid tablet);
- Drug not stored as instructed (e.g. kept in the fridge when it should be at room temperature);
- Wrong participant received the medication (excluding IVRS/IWRS errors);
- Wrong drug administered to participant (excluding IVRS/IWRS errors).

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error;
- Participant accidentally missed drug dose(s) e.g. forgot to take medication;
- Accidental overdose (will be captured as an overdose);
- Participant failed to return unused medication or empty packaging;
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product.

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of human biological samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at the site keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

The investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International airline transportation association (IATA) 6.2 guidance document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dgr/pages/index.aspx)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens (for example Ebola virus and Lassa fever virus) are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens include hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following United Nations (UN) number and proper shipping name:

- UN3373 – Biological Substance, Category B.
- Are to be packed in accordance with UN3373 and IATA 650.

Exempt - all other materials with minimal risk of containing pathogens.

- Clinical study samples will fall into Category B or Exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650-compliant packaging **(http://www.iata.org/whatwedo/cargo/dgr/pages/index.aspx).**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.**
- IATA-compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. Compliance with the IATA 650 biological sample containment standards is encouraged wherever possible when road or rail transport is used.

Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and HL cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated total bilirubin from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the IMP.

The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

PHL

AST or ALT≥3×ULN **together with** total bilirubin ≥2×ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

HL

AST or ALT≥3×ULN **together with** total bilirubin ≥2×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases (e.g. elevated ALP indicating cholestasis, viral hepatitis, another drug).

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

D 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3×ULN.
- AST ≥3×ULN.
- Total bilirubin ≥2×ULN.

The investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative.
- Determine whether the subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

D 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment.

- Notify the AstraZeneca representative who will then inform the central study team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition.
- The study physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
  - Complete follow-up SAE form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study physician.
  - Complete the 3 liver eCRF modules as information becomes available.
  - A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the study physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than drug-induced liver injury caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria were met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and total bilirubin elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF;
- If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and total bilirubin elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory. Any test results need to be recorded.

Table 14 Recommended Hy's Law laboratory tests

Additional standard chemistry and coagulation tests	Gamma-glutamyl transferase
	Lactate dehydrogenase
	Prothrombin time
	International normalised ratio
Viral hepatitis	IgM anti-hepatitis A virus
	IgM and IgG anti-HBc
	HBsAg
	HBV DNA
	IgG anti-HCV
	HCV RNA[a]
	IgM anti-hepatitis E virus
	Hepatitis E RNA
Other viral infections	IgM and IgG anti-cytomegalovirus
	IgM and IgG anti-herpes simplex virus
	IgM and IgG anti-Epstein-Barr virus
Alcoholic hepatitis	Carbohydrate deficient transferrin
Autoimmune hepatitis	Antinuclear antibody
	Anti-liver/kidney microsomal antibody
	Anti-smooth muscle Antibody
Metabolic diseases	Alpha-1-antitrypsin
	Ceruloplasmin
	Iron
	Ferritin
	Transferrin
	Transferrin saturation

Anti-HBc=hepatitis B core antibody; DNA=deoxyribonucleic acid; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; Ig=immunoglobulin; RNA=ribonucleic acid.

[a] HCV RNA is only tested when IgG anti-HCV is positive or inconclusive.

Appendix E Guidance for management of specific adverse events in adults and paediatric patients

E 1 Management of Left Ventricular Ejection Fraction (LVEF) Reduction (asymptomatic) or Left Ventricular Systolic Dysfunction (LVSD)

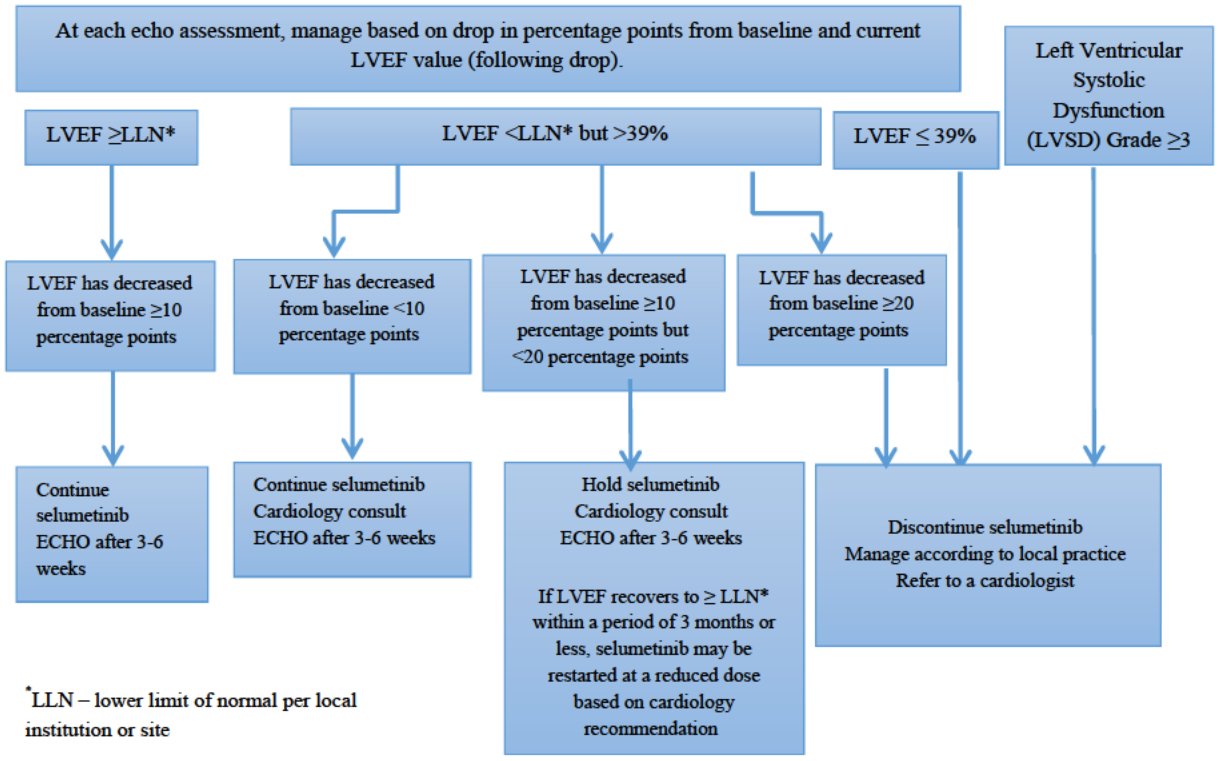


Table 15 CTCAE (version 5) grading for LVEF reduction and LVSD

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >=20% drop from baseline	Resting ejection fraction (EF) <20%	-
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death

E 2 Management of creatine kinase (CK) elevation

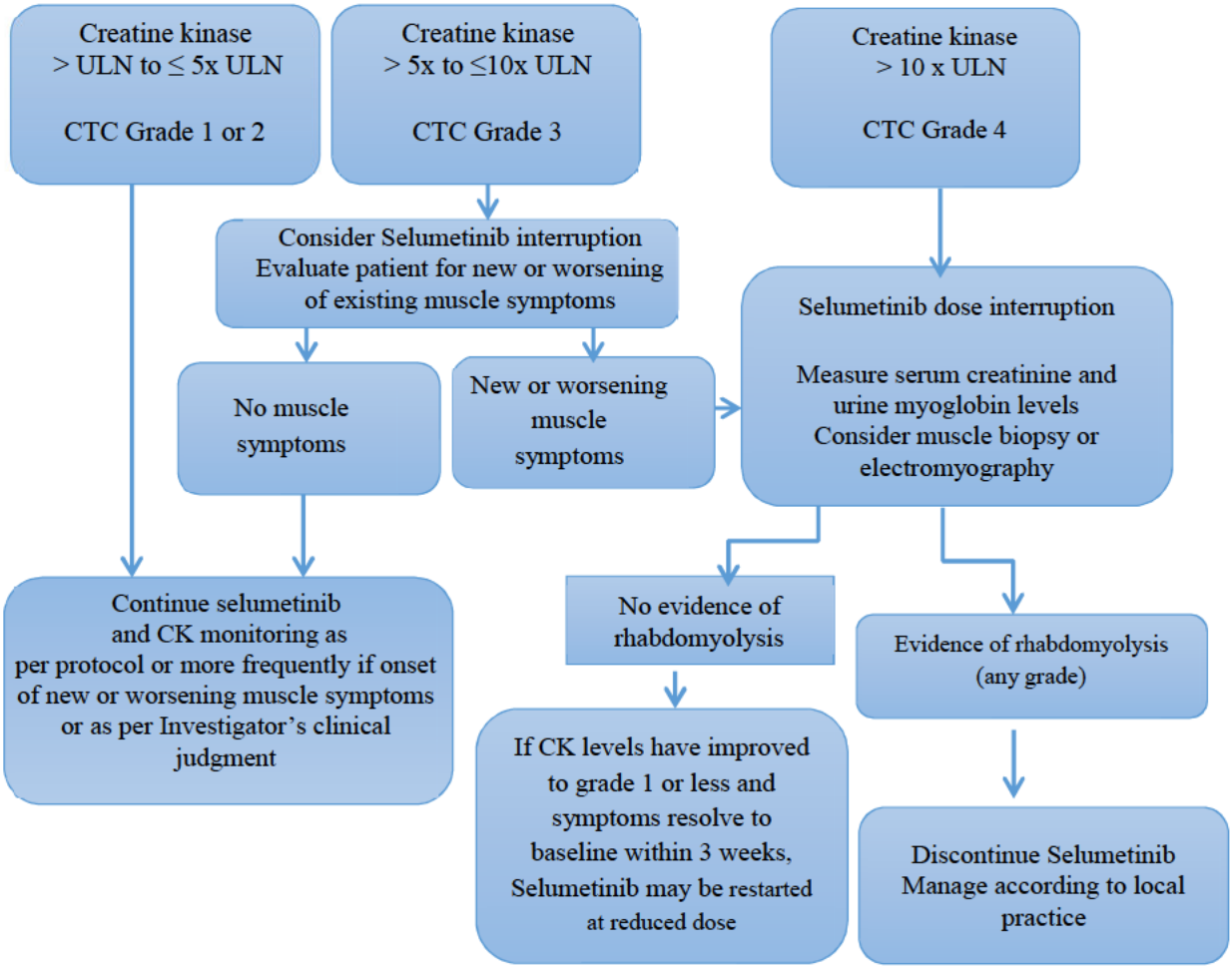
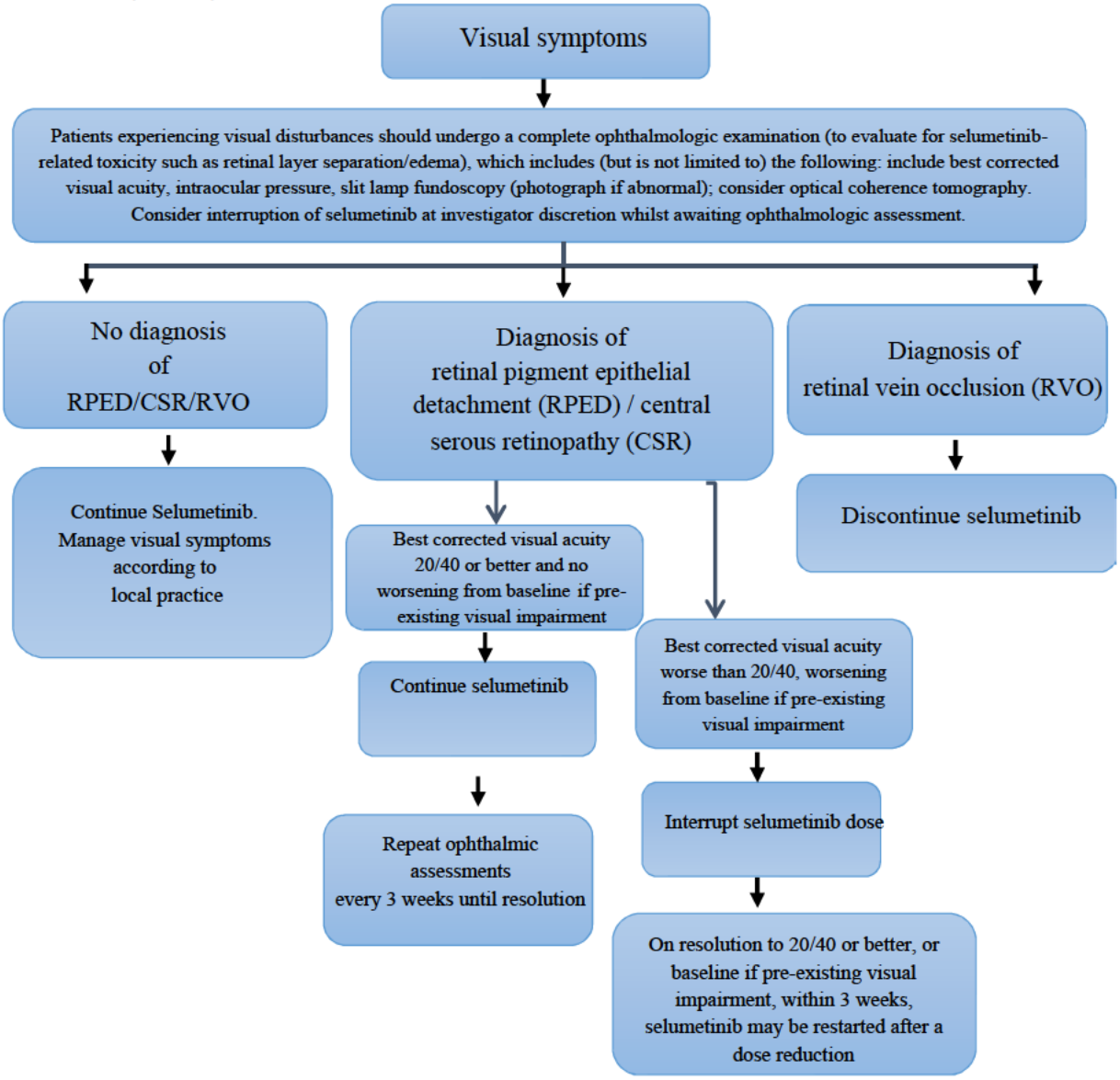


Table 16 CTCAE (version 5) grading for CPK increased and rhabdomyolysis

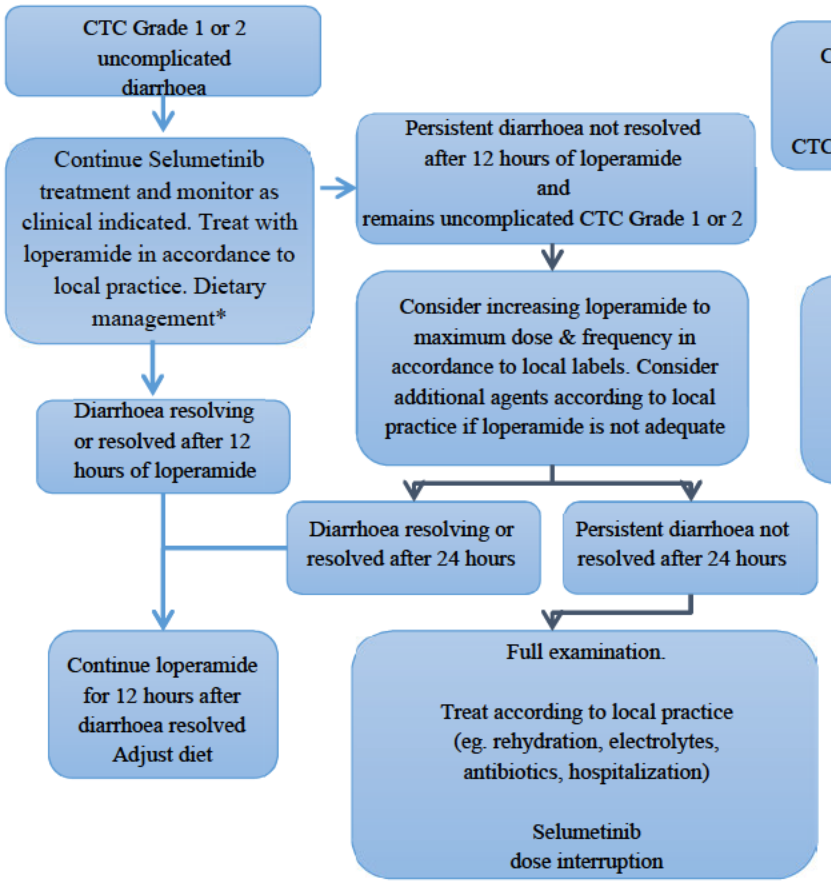
CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Rhabdomyolysis	Asymptomatic, intervention not indicated; laboratory findings only	Non-urgent intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; dialysis	Death

E 3 Management of Retinal Pigment Epithelial Detachment (RPED), Central Serous Retinopathy (CSR) and Retinal Vein Occlusion (RVO)



CSR=central serous retinopathy; RPED=retinal pigment epithelial detachment; RVO=retinal vein occlusion.

E 4 Management of diarrhoea



*BRAT diet (bananas, rice, apple sauce, toast, plain pasta), readily digestible food, avoidance of lactose-containing products and fried, fatty or spicy foods, increased fluid intake (8-10 glasses of clear fluids/day (including water, clear broth, fluids containing salt and sugar).
**Diarrhoea complicated by associated vomiting or inability to take oral fluids; marked abdominal distension or cramping; bloody stools, fever or symptoms of hypotension.

Table 17 CTCAE (version 5) grading for diarrhoea

Grade 1	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.
Grade 2	Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL (Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc).
Grade 3	Increase of ≥7 stools per day over baseline; hospitalisation indicated; severe increase in ostomy output compared to baseline; limiting self care ADL (self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death.

E 5 Management of New or Worsening Dyspnoea

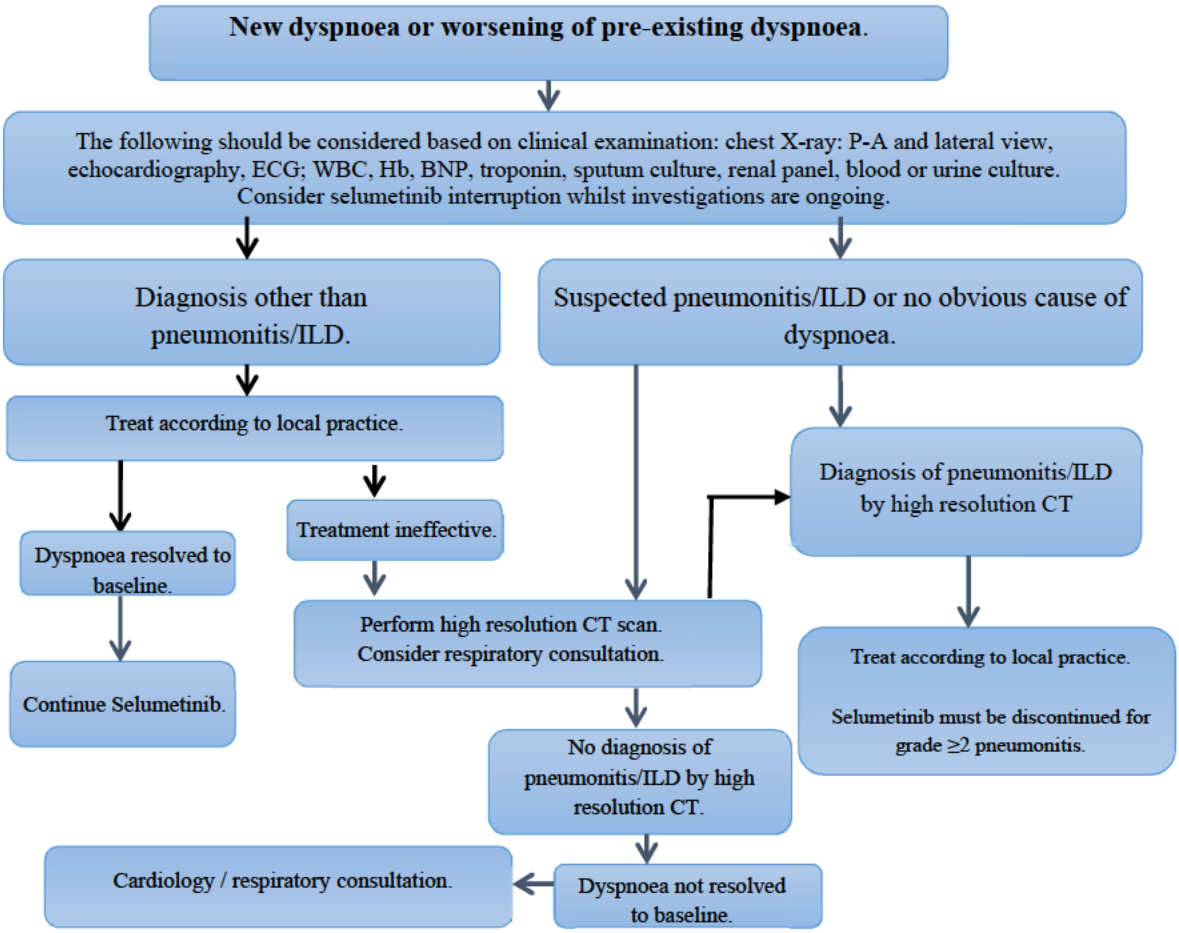


Table 18 CTCAE (version 5) grading for pneumonitis

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL*	Severe symptoms; limiting self care ADL**; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

E 6 Management of subjects with rash

Table 19 Management of Rash

Severity	Management STEP 1	Management STEP 2
CTC Grade 1 or 2 Tolerable Rash	Continue Selumetinib treatment and monitor as clinical indicated. Manage rash as per paediatric or adult treatment recommendations.	-
CTC Grade 2 Intolerable or CTC Grade≥3	Consider Selumetinib dose interruption. Consider referral to a dermatologist. Manage rash as per paediatric or adult treatment recommendations.	If rash has improved to Grade 2 tolerable or less within 4 weeks, re-start selumetinib at original dose or consider reduced dose.

Table 20 Rash - Paediatric Treatment Recommendations

Severity	Treatment Recommendations	Note
CTC Grade 1 Rash	Apply a mild potency topical steroid* and topical antibiotic**.	*Topical steroids e.g: 1% hydrocortisone or desonide cream for the face or 0.1% triamcinolone cream for the body (do not use on the face). **Topical antibiotics e.g: 1% Clindamycin gel, lotion, or solution. ***Oral tetracyclines e.g. doxycycline or minocycline (dosage regimens as per local guidelines). Doxycycline should be taken with food to avoid nausea. Minocycline should only be used if doxycycline is not tolerated. (tetracyclines should be avoided in children younger than 8 years because of risk to tooth discoloration).
CTC Grade 2 Rash (Tolerable)	Apply a moderate potency topical steroid* and initiate an oral antibiotic***. Topical antibiotics should be discontinued before initiation of oral antibiotics.	
CTC Grade 2 Rash (Intolerable) Or CTC Grade≥3	Apply a moderate potency topical steroid* and initiate an oral antibiotic***. Topical antibiotics should be discontinued before initiation of oral antibiotics. Follow toxicity management guidelines.	

Table 21 Rash - Adult Treatment Recommendations

Recommendations to start on day 1 of treatment with selumetinib and continue for the whole duration of treatment. • Apply a skin moisturiser (thick, alcohol-free) at bedtime. • Avoid excessive exposure to sunlight. • Avoid the use of topical retinoids or benzoyl peroxide, as these are not recommended.		
Severity	**Treatment Recommendations**	**Note**
CTC Grade 1 rash	Apply a mild/moderate strength topical steroid and/or topical antibiotic.	Example antibiotics and topical steroids (dosage regimens as per local guidelines): Topical steroids moderate strength e.g: Triamcinolone, Desonide, Aclometasone. Topical antibiotics e.g: Clindamycin, Erythromycin, Metronidazole, Silver sulphadiazine. Oral antibiotics e.g: Doxycycline, Minocycline, Oxytetracycline.
CTC Grade 2 rash (Tolerable)	Apply a moderate strength topical steroid and consider an oral antibiotic	
CTC Grade ≥3 rash or a CTC Grade 2 rash considered by the patient to be intolerable	Apply moderate strength topical steroid and consider an oral antibiotic. If an infection is suspected, consider other broad spectrum antibiotic cover.	

Table 22 CTCAE (version 5) grading for Rash relevant terms

(For other specific rash term, please refer to CTCAE guideline)

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL*	Widespread and constant; limiting self care ADL** or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-

Table 22 CTCAE (version 5) grading for Rash relevant terms

(For other specific rash term, please refer to CTCAE guideline)

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL*; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL**; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL*; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL**	-	-
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL*	Covering >30% BSA and associated with pruritus; limiting self care ADL**	-	-

Table 22 CTCAE (version 5) grading for Rash relevant terms

(For other specific rash term, please refer to CTCAE guideline)

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-	-

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

E 7 Oral Care management for events of oral mucositis and dry mouth

- Patients should be encouraged to follow a daily oral health care regimes, both before and during treatment with selumetinib.
- Patients with a healthy mouth may use non alcoholic mouthwash 4 to 6 times daily (e.g. after each meal), or according to the instructions, during the study.
- Saline mouthwashes (Sodium chloride 0.9%) are preferred to alcohol-based mouth washes in cases of stomatitis, and should be used at a different time than toothbrushing (e.g. after tea).
- Use of a mouthwash immediately after selumetinib intake is recommended.
- The tongue can be gently brushed (if not sore) with a soft toothbrush.
- Patients with, or at risk of, stomatitis should not use commercial/over-the-counter mouthwashes because of the alcohol content and astringency. Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis.
- The mouth should be regularly inspected by the patient and healthcare professionals.
- Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. The toothbrush should be replaced regularly (at least every 3 months). Patients with stomatitis should change their toothbrush every 4 - 6 weeks.
- Consider culture to rule out herpes simplex.
- Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the patient complains of a sore mouth. Consider using an oral topical analgesic, with or without topical steroids, depending on the patient's clinical condition and the local standard medical practice.

E 8 Management of Paronychia

Table 23 Management of Paronychia

Severity	Management STEP 1	Management STEP 2
CTC Grade 1 or 2 Tolerable Paronychia	Continue Selumetinib treatment and monitor as clinical indicated. Manage paronychia as per treatment recommendations.	-
CTC Grade 2 Intolerable or CTC Grade≥3	Consider Selumetinib dose interruption. Consider referral to a dermatologist. Manage paronychia as per treatment recommendations.	If paronychia has improved to Grade 2 tolerable or less within 4 weeks, re-start selumetinib at original dose or consider reduced dose.

Table 24 CTCAE (version 5) grading for paronychia

CTCAE term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL*.	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL**.	-	-

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Table 25 Treatment Recommendations for AE Paronychia*

Severity	Treatment Recommendations
CTCAE grade 1	Treat the affected area by soaking in vinegar solution twice daily (1 part vinegar to 2 parts water) + Topical Antibiotic mupirocin twice daily.
CTCAE grade 2	Treat the affected area by soaking in vinegar solution twice daily (1 part vinegar to 2 parts water) + Systemic antibiotic (Keflex, Clindamycin)+ high potency steroid (0.05% clobetasol ointment covered with saran wrap OR flurandrenolide tape (cordran tape) applied at bedtime. This should be removed in morning.
CTCAE grade 3	If severe, seek consult for incision & drainage or surgical management.
* If granulation tissue present, consider use of silver nitrate under supervision.	

For patients who do not undergo drainage, silver nitrate may be used, as well as topical bactroban, steroids, and/or antifungals. Silver nitrate is only of value when there is open inflamed skin or granulation tissue (e.g. pyogenic-granuloma-like lesions). If the periungual

skin is swollen but intact (whether infectious or non-infectious), silver nitrate is not recommended.

Patients should be cautioned to avoid trauma to the area. Podiatry consult may be considered for partial nail removal.

Patients who undergo incision and drainage and are found to have no infectious organisms on culture, should be treated as above. If infection is identified, patients may be treated with systemic antibiotics (oral tetracyclines).

If paronychia recurs or develops in other fingers or toes, Flurandrenolide (e.g. Cordran) tape or topical steroid cream such as triamcinolone can be used in the morning and Bactroban and Nizoral topical ointments in the evening.

Appendix F Blood pressure

Blood pressure ≤ the 95th percentile for age, height, and gender is required for enrolment. Because measurement accuracy is dependent on the use of proper BP cuff size, BP cuff should be selected as follows:

- Infant 8 to 11 cm.
- Child 12 to 16 cm.
- Small adult 17 to 22 cm.
- Adult 23 to 33 cm.

Table 26 Blood pressure levels for children by age and height percentile – blood pressure for boys

Age (years)	BP percentile	Systolic blood pressure (mmHg)							Diastolic blood pressure (mmHg)						
		Percentile of height							Percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
2	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
3	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
4	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
5	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
6	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
7	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
8	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
9	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
10	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
11	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
12	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
13	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
14	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
15	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
16	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
≥17	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89

BP=blood pressure.
Source: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004.

Table 27 Blood pressure levels for children by age and height percentile – blood pressure for girls

Age (years)	BP percentile	Systolic blood pressure (mmHg)							Diastolic blood pressure (mmHg)						
		Percentile of height							Percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
2	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
3	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
4	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
5	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
6	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
7	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
8	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
9	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
10	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
11	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
12	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
13	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
14	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
15	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
16	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
≥17	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86

BP=blood pressure.
Source: National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004.

Table 28 Canadian Cardiovascular Society grading of angina pectoris

Grade	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

Source: Campeau 1976.

Table 29 New York Heart Association classification

New York Heart Association grading		Metabolic equivalent[a]
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2 to 3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

CHF=congestive heart failure; LV=left ventricular; VO_2=maximal oxygen uptake.

[a] Metabolic equivalent is defined as the resting VO_2 for a 40-year-old 70 kg man. Metabolic equivalent = 3.5 mL O_2/min/kg body weight.

Appendix G Performance status scales

Table 30 Performance status criteria

Karnofsky (>16 years of age)		Lansky (≤16 years of age)	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalisation indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalisation indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Karnofsky and Lansky performance scores are intended to be multiples of 10.

Appendix H Medications to avoid

Strong or moderate inducers of CYP3A4 as well as strong or moderate inhibitors of CYP3A4 or CYP2C19 are not recommended at any time during the study. During the first cycle concomitant use of strong or moderate inhibitors of CYP3A4 or CYP2C19 should be avoided until after the PK assessment. During the remainder of the study, if concomitant use of selumetinib with strong or moderate CYP3A4 or CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Table 31 and the patient should be monitored closely for potential toxicities. The dose of selumetinib should be reduced for the duration of concomitant therapy with the strong or moderate CYP3A4 or CYP2C19 inhibitor. After the washout for 5 half-lives of the inhibitor is complete, the selumetinib dose can be re-escalated.

Table 31 Recommended Dosage of Selumetinib for Co-administration with Strong or Moderate CYP3A4 or CYP2C19 Inhibitors

Body Surface Area	If the current dosage is up to 25 mg/m^2 twice daily, reduce to 20 mg/m^2 twice daily (mg/dose)		If the current dosage is up to 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 daily	
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

Note. for patients with BSA 0.55 to 0.69 m^2, dose reduction is only applicable if the starting dose for this group is 20 mg in the morning and 10 mg in the evening.

Changes to, or addition of medications detailed in Table 32 and Table 33 should be avoided, unless clinically indicated.

Table 32 Inhibitors of CYP2C19 or CYP3A4

CYP2C19	CYP3A4
fluconazole	Indinavir
fluvoxamine	Nelfinavir
fluoxetine and ticlopidine	Ritonavir
	Clarithromycin

Table 32 Inhibitors of CYP2C19 or CYP3A4

CYP2C19	CYP3A4
	Itraconazole
	Ketoconazole
	Nefazodone
	Saquinavir
	Suboxone
	Telithromycin
	Aprepitant
	Erythromycin
	Fluconazole
	Grapefruit juice
	Verapamil
	Diltiazem

Table 33 Inducers of CYP3A4

CYP3A4
Efavirenz
Nevirapine
Barbiturates
Carbamazepine
Glucocorticoids
Modafinil
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
Rifampin
St John's wort
Troglitazone

Appendix I Clinical outcome assessments

These PRO questionnaires are for information purposes and representation only and serve as an example of the questionnaire to be used in the study.

FLACC scale

FLACC Pain Assessment Tool

Categories	Score 0	Score 1	Score 2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid, or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, hugging, or being talked to, distractable	Difficult to console or comfort

Merkel, S., Voepel-Lewis, T., Shayevitz, J., & Malviya, S. (1997). The FLACC: A behavioral scale for scoring postoperative pain in young children.

Pediatric Nursing 23(3), 293-297.

E-code: _____

Assessment Date: _____ Enter FLACC Total Score:____

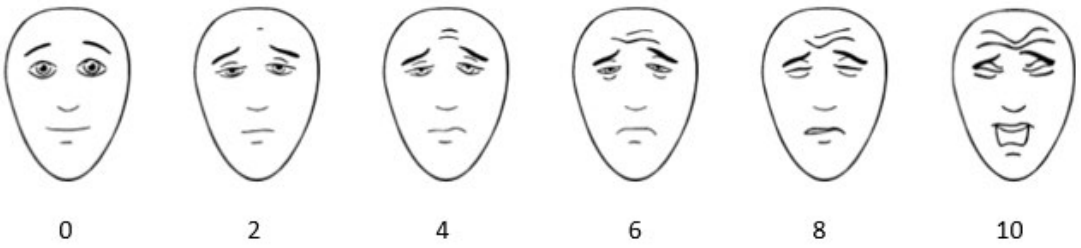
Assessment Time: _____

Initials of person administering the assessment: _____

Faces Pain Scale - Revised

Instructions

These faces show how much something can hurt. The face to the left shows no pain. The faces show more and more pain up to the right face - it shows very much pain. Please choose the face that shows the worst pain you had during the past week.



Source: Adapted from Hicks et al 2001.

NRS-11

Adult Pain Questionnaire

(Self-report form for adults)

Numeric Rating Scale – Pain Intensity

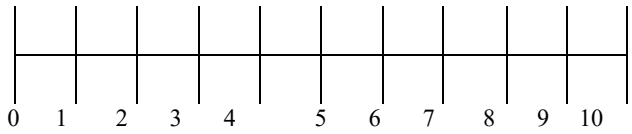
Below are some questions about how much you hurt. The first two questions are about how much your plexiform neurofibroma tumor or tumors hurt and the last question is about how much you hurt from all kinds of pain.

Below are lines with numbers from 0 to 10 where 0 means no pain and 10 means the worst pain you can imagine.

1. The doctor has picked the plexiform neurofibroma tumor in your body to measure for this study. We call this the "target tumor." We will ask you to tell us about that same tumor pain at each study visit.

Target tumor: _____

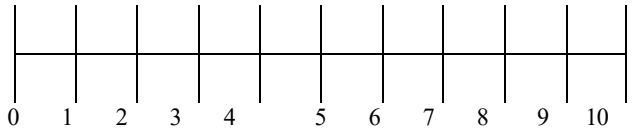
Please circle the one number that best describes the pain from your target tumor at its **worst** during the past 7 days.



No pain — Worst pain you can imagine

2. Do you have tumor pain in more than one place on your body? □ Yes □ No

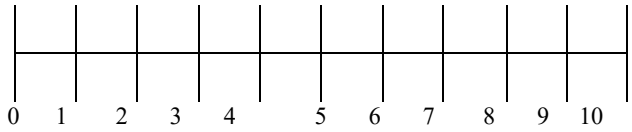
If yes, please circle the one number that best describes your overall tumor pain at its **worst** during the past 7 days.



No pain — Worst pain you can imagine

3. Do you have other kinds of pain (for example, headaches or back pain)? □ Yes □ No

If yes, please circle the one number that best describes your overall pain at its **worst** during the past 7 days (including tumor pain and any other kinds of pain.)



No pain

Worst pain you can imagine

Pain Interference Index

Self-report

Child/Adolescent Pain Questionnaires

(Self-report form for ages 8 – 18 years)

Pain Interference Index

Below you will find a list of questions about you and your pain. Please answer each question by circling one number between 0 and 6.

We are asking about your pain during the past 7 days.

In the past 7 days:

		Not at all						Some Completely
1.	Has your pain made it hard for you to pay attention (for example, do classwork, homework, read)?	0	1	2	3	4	5	6
2.	Has your pain made it hard for you to do things outside of school (play/ free time activities)?	0	1	2	3	4	5	6
3.	Has your pain made it hard for you to spend time with friends?	0	1	2	3	4	5	6
4.	Has your pain affected your mood?	0	1	2	3	4	5	6
5.	Has your pain made it hard for you to do physical activities (like run, walk up stairs, play sports, do chores)?	0	1	2	3	4	5	6
6.	Has your pain made it hard for you to sleep?	0	1	2	3	4	5	6

Adapted by the Health Psychology and Neurobehavioral Research Group, NCI (10/28/15)

Parent report

Parent Pain Questionnaires

(Parent report form for children ages 5 – 18 years)

Pain Interference Index

Below you will find a list of questions about your child. Please answer each question by circling one number between 0 and 6.

We are asking about your child's pain during the past 7 days.

In the past 7 days:

		Not at all				Some		Completely
1.	Has your child's pain made it difficult for your child to pay attention (for example, do classwork, homework, read)?	0	1	2	3	4	5	6
2.	Has your child's pain made it difficult for your child to do things outside of school (play/free time activities)?	0	1	2	3	4	5	6
3.	Has your child's pain made it difficult for your child to spend time with friends?	0	1	2	3	4	5	6
4.	Has your child's pain affected your child's mood?	0	1	2	3	4	5	6
5.	Has your child's pain affected your child's ability to do physical activities (like run, walk up stairs, play sports, do chores)?	0	1	2	3	4	5	6
6.	Has your child's pain affected your child's sleep?	0	1	2	3	4	5	6

Lab Matrix Form

Adult report

Pain Interference Index - Adult

Below you will find a list of questions about you and your pain. Please answer each question by circling one number between 0 and 6.

Please note that we are asking about your situation during the past week.

Has your pain:		Not at all			Some			Completely
1.	made it difficult for you to work (in or outside the home)?	0	1	2	3	4	5	6
2.	made it difficult for you to do activities outside of work (leisure activities)?	0	1	2	3	4	5	6
3.	made it difficult for you to spend time with friends and family members?	0	1	2	3	4	5	6
4.	affected your mood?	0	1	2	3	4	5	6
5.	affected your ability to do physical activities (like run, walk up stairs, play sports, do chores)?	0	1	2	3	4	5	6
6.	affected your sleep?	0	1	2	3	4	5	6

Paticipant's ID:_____
Date:_____

Pain medication survey:

To be completed by the patient or patient care giver for all patients (all ages). Please collect daily and as needed pain medication for 1 week prior to randomisation Please include:

- Dates
- Pain medication name,dose and route
- Frequency

	Date: ___/___/____/	Date: ___/___/____/	Date: ___/___/____/	Date: ___/___/____/	Date: ___/___/____/	Date: ___/___/____/	Date: ___/___/____/
#1 medication name, dosage, route							
#2 medication name, dosage, route							
#3 medication name, dosage, route							
#4 medication name, dosage, route							
#5 medication name, dosage, route							

☐ No pain medications used

completed by: _____ Date:_____

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____
Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

TEEN REPORT (ages 13-18)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL-Acute-Version-Adolescent_(Self Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

*In the past **7 days**, how much of a problem has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other teens	0	1	2	3	4
2. Other teens do not want to be my friend	0	1	2	3	4
3. Other teens tease me	0	1	2	3	4
4. I cannot do things that other teens my age can do	0	1	2	3	4
5. It is hard to keep up with my peers	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

PedsQL-Acute-Version-Adolescent_(Self Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for CHILDREN (ages 8-12)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL-Acute-Version-Child_(Parent Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

*In the past **7 days**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

PedsQL-Acute-Version-Child_(Parent Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____
Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

CHILD REPORT (ages 8-12)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for you. Please tell us **how much of a problem** each one has been for you during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL-Acute-Version-Child_(Self Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

*In the past **7 days**, how much of a problem has this been for you …*

ABOUT MY HEALTH AND ACTIVITIES *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard for me to walk more than one block	0	1	2	3	4
2. It is hard for me to run	0	1	2	3	4
3. It is hard for me to do sports activity or exercise	0	1	2	3	4
4. It is hard for me to lift something heavy	0	1	2	3	4
5. It is hard for me to take a bath or shower by myself	0	1	2	3	4
6. It is hard for me to do chores around the house	0	1	2	3	4
7. I hurt or ache	0	1	2	3	4
8. I have low energy	0	1	2	3	4

ABOUT MY FEELINGS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I feel afraid or scared	0	1	2	3	4
2. I feel sad or blue	0	1	2	3	4
3. I feel angry	0	1	2	3	4
4. I have trouble sleeping	0	1	2	3	4
5. I worry about what will happen to me	0	1	2	3	4

HOW I GET ALONG WITH OTHERS *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. I have trouble getting along with other kids	0	1	2	3	4
2. Other kids do not want to be my friend	0	1	2	3	4
3. Other kids tease me	0	1	2	3	4
4. I cannot do things that other kids my age can do	0	1	2	3	4
5. It is hard to keep up when I play with other kids	0	1	2	3	4

ABOUT SCHOOL *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. It is hard to pay attention in class	0	1	2	3	4
2. I forget things	0	1	2	3	4
3. I have trouble keeping up with my schoolwork	0	1	2	3	4
4. I miss school because of not feeling well	0	1	2	3	4
5. I miss school to go to the doctor or hospital	0	1	2	3	4

PedsQL-Acute-Version-Child_(Self Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for TEENS (ages 13-18)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for your teen. Please tell us **how much of a problem** each one has been for your teen during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL-Adolescent_(Parent-Proxy Reported)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

*In the past **7 days**, how much of a **problem** has your teen had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores around the house	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other teens	0	1	2	3	4
2. Other teens not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other teens	0	1	2	3	4
4. Not able to do things that other teens his or her age can do	0	1	2	3	4
5. Keeping up with other teens	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with schoolwork	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for TODDLERS (ages 2-4)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for your child. Please tell us how much of a problem each one has been for your child during the past 7 days by circling:

0 if it is never a problem
1 if it is almost never a problem
2 if it is sometimes a problem
3 if it is often a problem
4 if it is always a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

PedsQL-Toddler_(Parent-Proxy_Reported)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

*In the past **7 days**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

PedsQL-Toddler_(Parent-Proxy_Reported)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____

Date: _____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for YOUNG CHILDREN (ages 5-7)
Acute Version

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past 7 days** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

*In the past **7 days**, how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking more than one block	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in sports activity or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Taking a bath or shower by him or herself	0	1	2	3	4
6. Doing chores, like picking up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying about what will happen to him or her	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Getting along with other children	0	1	2	3	4
2. Other kids not wanting to be his or her friend	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

SCHOOL FUNCTIONING *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Paying attention in class	0	1	2	3	4
2. Forgetting things	0	1	2	3	4
3. Keeping up with school activities	0	1	2	3	4
4. Missing school because of not feeling well	0	1	2	3	4
5. Missing school to go to the doctor or hospital	0	1	2	3	4

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL

ID# _____

Date:_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

YOUNG CHILD REPORT (ages 5-7)
Acute Version

Instructions for the interviewer:

I am going to ask you some questions about things that might be a problem for some children. I want to know how much of a problem any of these things might be for you.

Show the child the template and point to the responses as you read.

If it is <u>not at all</u> a problem for you, point to the smiling face

If it is <u>sometimes</u> a problem for you, point to the middle face

If it is a problem for you <u>a lot</u>, point to the frowning face

I will read each question. Point to the pictures to show me how much of a problem it is For you. Let's try a practice one first.

	Not at all	Sometimes	A lot
Is it hard for you to snap your fingers	☺	😐	☹

Ask the child to demonstrate snapping his or her fingers to determine whether or not the question was answered correctly. Repeat the question if the child demonstrates a response that is different from his or her action.

PedsQL-Young Child_(Self-Report)_V4.0_Orig_WS_Paper_English_US_03Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PedsQL 2

Think about how you have been doing for the past 7 days. Please listen carefully to each sentence and tell me how much of a problem this is for you.

After reading the item, gesture to the template. If the child hesitates or does not seem to understand how to answer, read the response options while pointing at the faces.

PHYSICAL FUNCTIONING *(problems with…)*	Not At all	Some-times	A lot
1. Is it hard for you to walk	0	2	4
2. Is it hard for you to run	0	2	4
3. Is it hard for you to play sports or exercise	0	2	4
4. Is it hard for you to pick up big things	0	2	4
5. Is it hard for you to take a bath or shower	0	2	4
6. Is it hard for you to do chores (like pick up your toys)	0	2	4
7. Do you have hurts or aches (*Where?*_____)	0	2	4
8. Do you ever feel too tired to play	0	2	4

Remember, tell me how much of a problem this has been for you for the past 7 days.

EMOTIONAL FUNCTIONING *(problems with…)*	Not At all	Some-times	A lot
1. Do you feel scared	0	2	4
2. Do you feel sad	0	2	4
3. Do you feel mad	0	2	4
4. Do you have trouble sleeping	0	2	4
5. Do you worry about what will happen to you	0	2	4

SOCIAL FUNCTIONING *(problems with…)*	Not At all	Some-times	A lot
1. Is it hard for you to get along with other kids	0	2	4
2. Do other kids say they do not want to play with you	0	2	4
3. Do other kids tease you	0	2	4
4. Can other kids do things that you cannot do	0	2	4
5. Is it hard for you to keep up when you play with other kids	0	2	4

SCHOOL FUNCTIONING *(problems with…)*	Not At all	Some-times	A lot
1. Is it hard for you to pay attention in school	0	2	4
2. Do you forget things	0	2	4
3. Is it hard to keep up with schoolwork	0	2	4
4. Do you miss school because of not feeling good	0	2	4
5. Do you miss school because you have to go to the doctor's or hospital	0	2	4

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

EORTC QLQ-C30 (adult cohort only)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day!	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated	1	2	3	4

Please go on to the next page

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

During the past week:	Not at All	A Little	Quite a bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

PlexiQoL (adult cohort only)

PlexiQol

PLEASE READ THIS CAREFULLY

On the following pages you will find some statements that have been made by people with plexiforms.

As you are aware, plexiforms are tumours that grow on nerves underneath the skin. They are different from the tumours you find on your skin.

We would like you to tick 'True' if the statement applies to you and tick 'Not True' if it does not.

Please choose the response that applies best to you

AT THE MOMENT

PlexiQol_V1_Orig_WS_Paper_English_GB_04Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

Please read statement carefully and decide whether your plexiform(s) affect you in this way ***at the moment***

1. I avoid crowds where possible — True ☐ Not True ☐
2. I am unable to join in activities with my family and friends — True ☐ Not True ☐
3. I'm losing my role in life — True ☐ Not True ☐
4. I am reluctant to leave the house — True ☐ Not True ☐
5. I avoid looking at myself in the mirror — True ☐ Not True ☐
6. I feel I have no control over the plexiform(s) — True ☐ Not True ☐
7. I find the plexiform(s) ugly — True ☐ Not True ☐
8. I take out my anger on people close to me — True ☐ Not True ☐

Please turn over

PlexiQol_V1_Orig_WS_Paper_English_GB_04Sep2019_D1346C00011

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

Please remember to *tick only one* of the alternative responses for each of the statements

9. I avoid intimate situations — True ☐ Not True ☐

10. I find social situations stressful — True ☐ Not True ☐

11. I can't take care of myself — True ☐ Not True ☐

12. I don't like being touched — True ☐ Not True ☐

13. I feel dependent on others — True ☐ Not True ☐

14. I cover up the plexiform(s) — True ☐ Not True ☐

15. The quality of my relationships is affected — True ☐ Not True ☐

16. It's difficult to plan ahead — True ☐ Not True ☐

Study Number: D1346C00011		Site Number:
Subject Number:	Visit Number:	Assessment Date:

Please read statement carefully and decide whether your plexiform(s) affect you in this way ***at the moment***

17. I am very self-conscious about the way I look — True ☐ Not True ☐

18. My choices in life are restricted — True ☐ Not True ☐

Thank you for taking the time to fill in this questionnaire.

Please check all of the pages to make sure that you have answered every statement.

PROMIS (Mobility)

Self-report (children)

PROMIS Pediatric Item Bank v2.0 – Mobility– Short Form 8a

Pediatric Mobility – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
[illegible]	I could do sports and exercise that other kids my age could do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I could get up from the floor	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I could keep up when I played with other kids	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I could move my legs	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I could stand up by myself	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I could stand up on my tiptoes	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I could walk up stairs without holding on to anything	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
[illegible]	I have been physically able to do the activities I enjoy most	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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Parent proxy form

PROMIS Parent Proxy Item Bank v2.0 – Mobility– Short Form 8a

Parent Proxy Mobility – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
PFmobil2r	My child could do sports and exercise that other kids his/her age could do.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil5r	My child could get up from the floor	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil4r	My child could keep up when he/she played with other kids	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil6r	My child could move his/her legs	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil3r	My child could stand up without help.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil7r	My child could stand up on his/her tiptoes	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil8r	My child could walk up stairs without holding on to anything.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFmobil1r	My child has been physically able to do the activities he/she enjoys most	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Last Updated: 29 July 2016
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PROMIS (upper extremity)

Self-report (children)

PROMIS® Pediatric Item Bank v2.0 – Upper Extremity – Short Form 8a

Pediatric Upper Extremity – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
3880R2r	I could button my shirt or pants	☐ 4	☐ 3	☐ 2	☐ 1	☐ 1
2671R1r	I could open a jar by myself	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
4143R1r	I could open the rings in school binders	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
4112R1r	I could pour a drink from a full pitcher	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
3881R1r	I could pull a shirt on over my head by myself	☐ 4	☐ 3	☐ 2	☐ 1	☐ 1
4130R1r	I could pull open heavy doors	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
2657bR1r	I could put on my shoes by myself	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
4109R1r	I could use a key to unlock a door	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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Parent proxy form

PROMIS® Parent Proxy Item Bank v2.0 – Upper Extremity– Short Form 8a

Parent Proxy Upper Extremity – Short Form 8a

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	With no trouble	With a little trouble	With some trouble	With a lot of trouble	Not able to do
Pf2uprext3r	My child could button his/her shirt or pants	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf4uprext1r	My child could open a jar by himself/herself	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf3uprext11r	My child could open the rings in school binders	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf4uprext10r	My child could pour a drink from a full pitcher	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf3uprext4r	My child could pull a shirt on over his/her head without help	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf3uprext9r	My child could pull open heavy doors	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf2uprext2r	My child could put on his/her shoes without help	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Pf3uprext7r	My child could use a key to unlock a door	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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PROMIS Physical Function - Short Form 8c 7-day; adult cohort

Self-report (adults)

PROMIS® Item Bank v2.0 – Physical Function – Short Form 8c 7-Day

Physical Function – Short Form 8c 7-Day

Please respond to each item by marking one box per row.

Thinking about the past 7 days...

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA87d	Are you able to bend down and pick up clothing from the floor?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA157d	Are you able to stand up from an armless straight chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r17d	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA217d	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA85r7d	Are you able to wash and dry your body?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA237d	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA17d	Does your health now limit you in doing vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		No difficulty at all	**A little bit of difficulty**	**Some difficulty**	**A lot of difficulty**	**Can't do because of health**
PFB50r7d	How much difficulty do you have doing your daily physical activities, because of your health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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Patient Global Impression of Severity (Self Report)

Think about your tumour pain. Overall, how would you rate the severity of your tumour pain today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Now think about all the different kinds of pain you may have. Overall, how would you rate the severity of your overall pain today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Think about your tumour-related problems other than pain (such as moving, vision, hearing, appearance, etc.). Overall, how would you rate the severity of your tumour-related problems today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Patient Global Impression of Severity (Parent Report)

Think about your child's tumour pain. Overall, how would you rate the severity of your child's tumour pain today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Now think about all the different kinds of pain your child may have. Overall, how would you rate the severity of your child's overall pain today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Think about your child's tumour-related problems other than pain (such as moving, vision, hearing, appearance, etc.). Overall, how would you rate the severity of your child's tumour-related problems today?

☐ No symptoms

☐ Very mild

☐ Mild

☐ Moderate

☐ Severe

☐ Very Severe

Patient Global Impression of Change (PGIC) (Self Report)

Think about your tumour pain. Compared to before you started taking the medicine for this study, would you say your tumour pain is:

Please tick (ü) one box only:

c Much Better

c Moderately Better

c A Little Better

c About the Same

c A Little Worse

c Moderately Worse

c Much Worse

Now think about all the different kinds of pain you may have. Compared to before you started taking the medicine for this study, would you say your overall pain is:

Please tick (ü) one box only:

c Much Better

c Moderately Better

c A Little Better

c About the Same

c A Little Worse

c Moderately Worse

c Much Worse

Think about your tumour-related problems other than pain (such as moving, vision, hearing, appearance, etc.). Compared to before you started taking the medicine for this study, would you say your tumour-related problems are:

Please tick (ü) one box only:

c Much Better

c Moderately Better

c A Little Better

c About the Same

c A Little Worse

c Moderately Worse

c Much Worse

Patient GLOBAL Impression of Change (PGIC) (Parent Report)

Think about your child's tumour pain. Compared to before your child started taking the medicine for this study, would you say your child's tumour pain is:

Please tick (ü) one box only:

c Much Better

c Moderately Better

c A Little Better

c About the Same

c A Little Worse

c Moderately Worse

c Much Worse

Now think about all the different kinds of pain your child may have. Compared to before your child started taking the medicine for this study, would you say your child's overall pain is:

Please tick (ü) one box only:

c Much Better

c Moderately Better

c A Little Better

c About the Same

c A Little Worse

c Moderately Worse

c Much Worse

Think about your child's tumour-related problems other than pain (such as moving, vision, hearing, appearance, etc.). Compared to before your child started taking the medicine for this study, would you say your child's tumour-related problems are:

Please tick (ü) one box only:

c Much Better

c Moderately Better

c A Little Better

c About the Same

c A Little Worse

c Moderately Worse

c Much Worse

Appendix J Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the patient's safety. If in doubt, please contact the AZ Study Physician.

J 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Section . Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

J 2 Rescreening of Participants To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Section 1.1**,** the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant in addition to that detailed in Section 5.4**.** The

procedures detailed in Section 1.1, 5.1 and 5.2 must be undertaken to confirm eligibility using the same randomization number as for the participant.

J 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the participants home / or other remote location as per local standard operating procedures (SOPs), as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study protocol (CSP). [If applicable, assessments will be performed according to a revised Schedule of Assessments (SoA)].

J 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the participants will allow adverse events, concomitant medication, and other relevant data to be reported and documented.

J 5 At-home or Remote Location IP Administration Instructions (where applicable)

If a site visit is not possible, at-home or remote location administration of IP may be performed by a qualified HCP, provided this is acceptable within local regulation/guidance, or by the patient or his/her caregiver. The option of at-home or remote location IP administration ensures participants safety in cases of a pandemic where participants may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

J 5.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service (where applicable)

A qualified HCP from the study site or TPV service should administer the IP at the participant's home or other remote location according to the CSP. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

J 5.2 At-home or Remote Location IP Administration by the Participants or His/Her Caregiver (where applicable)

Prior to at-home or remote location IP administration the investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, he/she must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

J 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in source documents, or by the participant themselves.

J 7 COVID-19 Vaccination

Investigators should follow their local prescribing information and policies when considering if vaccination against COVID-19 is appropriate for their patients participating in an AstraZeneca clinical trial.

Please consider the following if you are considering vaccinating your patient against COVID-19:

For a specific vaccine, consider the potential impact of its relevant prescribing information (ie, Indications, Contraindications, Warnings and Precautions, Adverse Reactions) on its use in the study population.

For patients with flexibility as to when to be enrolled in an AstraZeneca-sponsored study, vaccination prior to first dose of the trial investigational product(s) may be advisable.

Please contact the individual COVID-19 vaccine manufacturer if you have any questions concerning their product.

To better assess the overall impact of COVID-19 vaccination on a particular study and study population, ensure that both the COVID-19 vaccination details (including brand name and manufacturer) is captured in the eCRF as concomitant medication, and adverse reactions are reported.

Appendix K Abbreviations

Abbreviation or special term	Explanation
ADL	Activities of daily living
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve from zero to infinity
AUC_{0-12}	Area under the concentration-time curve from zero to 12 hours
$AUC_{0-12,ss}$	Area under the concentration-time curve from zero to 12 hours at steady state
AUC_{0-t}	Area under the concentration-time curve from zero to the last measurable concentration
BID	Twice daily
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
CFR	Code of Federal Regulations
CI	Confidence intervals
CK	Creatine kinase
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum steady-state plasma concentration
CR	Complete response
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
CYP	Cytochrome P450
DCO	Data cut-off
DoR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
FLACC	Face, Legs, Activity, Cry, Consolability
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GCV	Geometric coefficient of variation
G_{mean}	Geometric mean
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCP	Health Care Professional
HL	Hy's Law
HRQoL	Health-related quality of life
IATA	International airline transportation association
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IMP	Investigational medicinal product
International Co-coordinating investigator	If a study is conducted in several countries the International Co-coordinating Investigator is the investigator coordinating the investigators and/or activities internationally.
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MEK	Mitogen activated protein kinase
MPNST	Malignant peripheral nerve sheath tumours
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCI	National Cancer Institute
NF1	Neurofibromatosis type 1
NIH	National Institutes of Health
NRS	Numeric Rating Scale
ORR	Objective response rate
PCR	Polymerase chain reaction

Abbreviation or special term	Explanation
PD	Progressive disease
PedsQL	Paediatric Quality of Life Inventory
PFS	Progression-free survival
PGIC	Patient's global impression of change
PGIS	Patient's global impression of severity
PHL	Potential Hy's Law
PII	Pain Interference Index
PK	Pharmacokinetic(s)
PlexiQoL	Plexiform neurofibromas quality of life scale
PN	Plexiform neurofibromas
PR	Partial response
PROMIS	Patient-Reported Outcomes Measurement Information System
QTcF	QT interval corrected by Fridericia's method
Rac	Accumulation ratio
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SRC	Safety Review Committee
$t_{1/2}$	Terminal half-life
t_{max}	Time to maximum plasma concentration
TTP	Time to progression
TTR	Time to response
TPV	Third-party vendor
ULN	Upper limit of normal
UN	United Nations
US	United States
WBDC	Web Based Data Capture

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