Clinical Study Protocol	
Study Intervention	Selumetinib
Study Code	D1346C00004
Version	5.0
Date	15 March 2024

EudraCT / EU CT Number	[2020-005608-20 / 2023-506357-38-00]

A Phase I/II, Single-Arm, Open-label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE)

Sponsor Name: AstraZeneca AB

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Regulatory Agency Identifier Number(s): IND 122851; EudraCT: 2020-005608-20; EU CT Number: 2023-506357-38-00

This 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: D1346C00004

Version Scope: 5.0

Amendment Number: 4.0

Study Intervention: Selumetinib

Brief Title: Pharmacokinetics, Safety and Efficacy of the Selumetinib Granule Formulation in Children aged ≥ 1 to < 7 Years with NF1-related Symptomatic, Inoperable PN (SPRINKLE).

Medical Monitor Name and Contact Information will be provided separately.

Study Phase: Phase I/II

Acronym: SPRINKLE

Pediatric Investigational Plan Number: EMEA-001585-PIP01-13

Study Clinical Lead Name and Contact Information will be provided separately.

International Coordinating Investigator: PPD

SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
CSP Version 5.0 (Amendment 4.0)	15-Mar-2024
CSP Version 4.0 (Amendment 3.0)	14-Feb-2023
CSP Version 3.0 (Amendment 2.0)	30-Nov-2022
CSP Version 2.0 (Amendment 1.0)	18-Mar-2022
CSP Version 1.0 (Original Protocol)	05-Aug-2021

Amendment 4.0 (15-Mar-2024)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13) because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The main purpose of the amendment is to ensure the CSP is aligned and compliant with the specifications required by the EU CTR. Clarifications have been made and other typographical errors have been corrected.

Summary of Non-substantial Changes

Section Number and Name	Description of Change	Brief Rationale
Section 8.1: Administrative and General/Baseline Procedures	Added this section, although it is blank in terms of content	Added to align the section numbers with most recent CSP template
Section 8.4.9: Reporting of Serious Adverse Events	Added the following wording “In the European Union, the Sponsor will comply with safety reporting requirements and procedures as de-scribed in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database with-in the required regulatory timelines.”	Added to align with EU CTR transition requirements

Section 8.4.11.1: Timelines	Added this section	Added to align the section numbers with most recent CSP template
Section 8.4.11.1: Timelines	Changed "If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one day**" to "If an event of medication error, drug abuse, or drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day"**	Added to align with EU CTR transition requirements
Appendix A 1: Regulatory and Ethical Considerations	Updated section regarding "Regulatory Reporting Requirements for Serious Breaches"	Added to align with EU CTR transition requirements
Appendix A 4: Data Protection	Added 2 bullet points: • The participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information. • The participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.	Added to align with most recent CSP template
Appendix A 4: Data Protection	Added subsection regarding "Personal Data Breaches"	Added to align with EU CTR transition requirements

Appendix A 5: Committee Structure	Added this section, although it is blank in terms of content	Added to align the section numbers with most recent CSP template
Appendix A 6: Dissemination of Clinical Study Data	Updated this section to include wording around submission to EU CTIS within a year from global End of Trial Date. Also added www.astrazenecaclinicaltrials.com link and https://euclinicaltrials.eu/ link	Added to align with EU CTR transition requirements
Appendix A 7: Data Quality Assurance	Updated last bullet point to change data retention policy from "15 years after study completion" to "a minimum of 25 years after study archiving"	Added to align with EU CTR transition requirements
Appendix B 4: Medication Error, Drug Abuse and Drug Misuse	Updated wording regarding examples of Medication Error	Updated to align with EU CTR transition requirements
Appendix G: Country Specific Requirement	Added this section	Added to align with EU CTR transition requirements
Appendix M: Protocol Amendment History	Updated this section to include Amendment 3.0 changes	Updated this section to include Amendment 3.0 changes

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase I/II Single-Arm, Open-Label Study to Evaluate the Pharmacokinetics, Safety/Tolerability and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 Years with Neurofibromatosis Type 1 (NF1) Related Symptomatic, Inoperable Plexiform Neurofibromas (PN) (SPRINKLE).

Short Title:

Pharmacokinetics, Safety and Efficacy of the Selumetinib Granule Formulation in Children Aged ≥ 1 to < 7 years with NF1-related Symptomatic, Inoperable PN (SPRINKLE).

Rationale:

Selumetinib (capsule formulation) is approved by the FDA for the treatment of paediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN and a Conditional Marketing Authorisation was granted in Europe/EEA for paediatric patients 3 years of age and older, via the European Centralised Procedure on 17 June 2021. The efficacy of selumetinib in the treatment of NF1-related inoperable PN in paediatric participants was demonstrated in the SPRINT study; safety data from this study showed that selumetinib has a manageable safety profile with favourable tolerability over several years of treatment in this population.

Selumetinib is currently available in a capsule formulation which precludes administration to children with a BSA of < 0.55 m^2 or very young children who may have difficulty swallowing capsules. Therefore, AstraZeneca has developed an alternative age appropriate granule formulation of selumetinib for infants and young children aged ≥ 1 to < 7 years which is contained within a sprinkle capsule.

The relative bioavailability of the granule and capsule formulations has been investigated in adult healthy male subjects (Study D1532C00089, Study 89); with a geometric mean ratio (90% CI) of 0.654 (0.581, 0.736) for dose-normalized Cmax and 0.865 (0.811, 0.922) for dose-normalized AUC. The selumetinib content in the granule formulation batch used in Study 89 was CCI% therefore, when corrected for selumetinib content, the granule AUC was only CCI% lower compared to capsule. The selumetinib content in the granule formulation which will be used in the SPRINKLE study will be approximately CCI%.

This study is designed to define a dosing regimen and assess the PK and safety of the granule formulation in children aged ≥ 1 to < 7 years; the study will also include descriptive analyses of exploratory efficacy endpoints. Assuming that the AUC for the granule formulation is similar to the AUC for the capsule formulation observed in SPRINT, efficacy in children aged

≥ 1 year can be extrapolated from the SPRINT study. The study will inform the benefit risk profile of the granule formulation in children aged ≥ 1 to < 7 years with NF1-related symptomatic, inoperable PN.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To determine the PK of selumetinib after administration of the selumetinib granule formulation.	• Selumetinib AUC0-12 derived after single dose administration.
• To assess the safety and tolerability of the selumetinib granule formulation.	• Safety and tolerability will be evaluated in terms of AEs, clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis), physical examination, weight, vital signs, ECG, ECHO, ophthalmologic assessment, knee (or wrist) MRI/X-ray, and performance status. • Assessments related to AEs will include: occurrence/frequency; relationship to study intervention; CTCAE grade; seriousness; death; AEs leading to discontinuation of study intervention; AEs of special interest.
Secondary	
• To assess the palatability of the selumetinib granule formulation	• Palatability will be assessed using the parent-reported observer palatability assessment.
• To further assess the PK of selumetinib and N-desmethyl selumetinib metabolite after administration of the selumetinib granule formulation.	• Plasma concentrations and PK parameters of selumetinib including, but not limited to: ◦ Selumetinib AUC0-12 derived after multiple dose administration. ◦ Cmax, AUC0-6, AUClast, CL/F, tmax, tlast derived after single and multiple dose administration. ◦ AUC0-24, Vz/F and t½λz after single dose administration. ◦ Rac Cmax, Rac AUC0-12, and Vss/F derived after multiple dose administration. • Plasma concentrations and PK parameters of N-desmethyl selumetinib including, but not limited to: ◦ Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after single and multiple dose administration. ◦ Rac Cmax and Rac AUC0-12 derived after multiple dose administration. ◦ Parent-to-metabolite ratio for AUC0-6, AUC0-12 and AUC0-24 (single dose only), and Cmax after single and multiple dose administration.

Objectives	Endpoints
• To evaluate the efficacy of the selumetinib granule formulation by assessment of ORR as determined by ICR per REiNS criteria.	• Objective Response Rate
Exploratory Objectives	
• To evaluate the efficacy of the selumetinib granule formulation by assessment of CCI CCI as determined by ICR per REiNS criteria.	• CCI • CCI • CCI • CCI
• To evaluate efficacy of the selumetinib granule formulation by assessment of CCI	• Parent-reported CCI CCI total score.
• To evaluate efficacy of the selumetinib granule formulation by assessment of CCI CCI	• CCI CCI CCI CCI.
• To evaluate the safety of the selumetinib granule formulation by assessment of CCI	• CCI to assess language, motor skills and cognitive functions in participants aged < 3.5 years. • CCI to assess language and cognitive functions in participants aged ≥ 3.5 years. • CCI CCI to assess motor skills in participants aged ≥ 3.5 years. • CCI.
• To evaluate the pharmacodynamic effect of selumetinib in PBMCs.	• Change from baseline in PD markers which may include but may not be limited to pERK
• To determine the PK of selumetinib and N-desmethyl selumetinib after administration of the selumetinib capsule formulation.	• Plasma concentrations and PK parameters of selumetinib including, but not limited to: ° Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after multiple dose administration. ° CL/F and VssF derived after multiple dose administration. • Plasma concentrations and PK parameters of N-desmethyl selumetinib including, but not limited to: ° Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after multiple dose administration. ° Parent to metabolite ratio for AUC0-6, AUC0-12, and Cmax after multiple dose administration. • For the participants that transition to capsule formulation, CCI AUC0-6, AUC0-12, AUClast and Cmax will be determined following multiple dose administration of granule and capsule formulation. The ratio of granule:capsule formulation will be determined for each of these parameters.

Objectives	Endpoints
• CCI analyses will be completed to investigate the selumetinib exposure-response relationship for safety, biomarkers and efficacy.	• CCI analyses will be completed to assess the effect of CCI on selumetinib granule and capsule PK, including all paediatric PK data available. In addition, if data allows, CCI analyses will be completed to investigate the selumetinib exposure-response relationship for safety, biomarkers and efficacy.
• To explore potential biomarkers in residual PK or PD samples, which may influence the progression of neurofibromatosis and inoperable PNs (and associated clinical characteristics) and/or identify participants likely to respond to selumetinib or, may be surrogate markers of response.	• Exploratory biomarker analysis that may include (but not limited to) change from baseline in the expression and activity of neurofibromatosis and MEK pathways and/or specific RNA transcripts (arrays) as a surrogate for protein expression.

AE, adverse event; AUC, area under the concentration time curve; AUC0-6, area under the concentration-time curve from time zero to 6 hours; AUC0-12, area under the concentration-time curve from time zero to 12 hours; AUC0-24, area under the concentration-time curve from time zero to 24 hours; AUClast, area under the concentration-time curve from time zero to time of last measurable concentration; CCI CCI; CL/F, apparent total clearance of the drug from plasma; Cmax, maximum peak plasma concentration; CTCAE, Common Terminology Criteria For Adverse Events; CCI; ECG, electrocardiogram; ECHO, echocardiogram; CCI CCI; CCI ICR, independent central review; MEK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; ORR, objective response rate; PBMC, peripheral blood mononuclear cells; PD, pharmacodynamic; CCI; PK, pharmacokinetics; PN, plexiform neurofibroma; Rac, relative accumulation ratio; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; RNA, ribonucleic acid CCI; $t_{½\lambda z}$, elimination half-life; tlast, time to last measurable concentration; tmax, time to maximum concentration; VssF, apparent volume of distribution at steady state after non-intravenous administration; Vz/F, apparent volume of distribution after non-intravenous administration.

Overall Design:

This is a Phase I/II, single-arm, open-label study in children aged ≥ 1 to < 7 years at study entry (date of ICF signature) with a clinical diagnosis of NF1-related symptomatic, inoperable PN. The study is designed to evaluate the PK, safety and tolerability of selumetinib given as a granule formulation (Figure 1).

Participants will receive selumetinib for 25 cycles (or until they meet discontinuation criteria).

Enrolment into the Global Cohorts (Cohorts 1 and 2) will be stratified by age group:

- Cohort 1: participants enrolled outside Japan aged between ≥ 4 and < 7 years
- Cohort 2: participants enrolled outside Japan aged between ≥ 1 to < 4 years

In addition to the Global Cohorts, Japanese participants in Japan aged between ≥ 1 to < 7 years with NF1 related symptomatic, inoperable PN will be enrolled into the Japan Cohort.

After completion of at least one cycle (28 days) of dosing in 3 evaluable participants in Cohort 1, SRC will review the emerging safety and PK data. Providing the single dose PK exposure is within the acceptable range and there are no safety concerns as determined by SRC then dosing in Cohort 2 will be initiated and additional participants will be dosed in Cohort 1 (Figure 2). If the PK exposure is not within the acceptable range, the dose schema may be adjusted to ensure that selumetinib exposure is within the range observed in the SPRINT study; PK will be assessed against acceptance criteria in an additional 3 evaluable cohort 1 participants who received the adjusted dose. Cohort 2 will be initiated once the selumetinib granule formulation dose schema is identified for Cohort 1. The physiologically-based PK model will be updated, if required, based on emerging PK data.

Additional SRC reviews will be held for each of the cohorts following at least one cycle of dosing in approximately 6 evaluable participants and again in approximately 10 evaluable participants. The SRC will evaluate the PK, safety and tolerability of the granule formulation for that dose schema. The Japan Cohort will not participate in the dose-finding phase.

Participants who are aged ≥ 5 years at the end of 25 cycles of selumetinib will be considered to have completed the study for data analysis purposes. Participants who terminate treatment prior to Cycle 25 will be followed up to collect MRIs performed as standard of care and details of NF1-PN treatment information until the time when they would have completed 25 cycles of treatment, or they commence an alternative systemic NF1-PN treatment, whichever is the earliest. Any participant who is aged < 5 years after 25 cycles of selumetinib (or when they terminate treatment with selumetinib) will enter a safety follow-up phase. Participation in the safety follow-up will continue until they reach the age of 5 years or commence an alternative systemic NF1-PN treatment, whichever is the earlier. Participants can continue to receive selumetinib (capsule or sprinkle capsule) during the safety follow-up as long as they are considered to be receiving benefit in the opinion of their Investigator.

Continued Access to Study Intervention after the End of the Study

The study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the participant's last visit, AstraZeneca will continue to supply selumetinib to participants whilst they are still receiving clinical benefit or until meeting any other discontinuation criteria.

AstraZeneca will continue to supply selumetinib in the continued access phase of this study while, in the opinion of the Investigator, the participant is benefiting.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final data cut-off (DCO) and database closure, participant(s) currently receiving treatment with selumetinib may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

Disclosure Statement: This is a single group treatment study with one arm that has no masking.

Number of Participants:

Global Cohorts (Cohorts 1 and 2)

Approximately CCI participants will be dosed in Cohorts 1 and 2 to achieve CCI evaluable participants at the recommended granule formulation dose schema, of whom at least CCI participants will be aged ≥ 1 to < 4 years (with at least CCI aged < 2 years) and at least CCI participants will be aged ≥ 4 to < 7 years at enrolment.

Japan Cohort

A minimum of CCI evaluable Japanese paediatric participants aged ≥ 1 to < 7 years with NF1 related symptomatic, inoperable PN will be enrolled and receive treatment in the Japan Cohort.

For Global and Japan Cohorts

An evaluable participant for PK and sample size calculations is defined as a participant with a PK profile on Day 1 without any important protocol deviations potentially impacting the PK results.

Note: "Enrolled" means a participant's legally authorised representative (parent or guardian) and participant's (if deemed appropriate as per local regulations) agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not receive selumetinib, are considered "screen failures", unless otherwise specified by the CSP.

Intervention Group and Duration:

This study consists of a screening period (up to 28 days), a treatment period (25 cycles) and a long term safety follow-up for participants until they are 5 years old or commence an

alternative systemic NF1-PN treatment, whichever is the earlier. Participants may continue treatment with selumetinib throughout the long term safety follow-up as long as they are considered to be receiving clinical benefit in the opinion of their Investigator. A safety follow-up assessment will be performed 30 days after the last dose of study intervention for all study participants.

Selumetinib will be administered using BSA-based dosing. The granule formulation dose schema to be used in the study will be established in the dose-finding phase.

At enrolment participants must have a BSA within the range 0.40 to 1.09 m^2; once participants attain a BSA between 1.10 and 1.29 m^2 they will be encouraged to transition to the capsule formulation, if feasible, although all participants must remain on the granule formulation until after they have completed their third cycle of treatment.

Data Monitoring Committee: No

Safety Review Committee: Yes

An SRC will be formed for the dose-finding phase of the study to evaluate the safety, tolerability and PK data of the selumetinib granule formulation. Detailed information will be provided in the SRC charter.

Statistical Methods

Sample Size

Global Cohorts (Cohorts 1 and 2)

Approximately CCI participants will be dosed in Cohorts 1 and 2 to achieve CCI evaluable participants at the recommended granule formulation dose schema, of whom at least CCI participants will be aged ≥ 1 to < 4 years (with at least CCI aged < 2 years) and at least CCI participants will be aged ≥ 4 to < 7 years. A sample size of CCI participants will provide reasonable precision to characterise PK and safety.

With a minimum of CCI evaluable participants in each age group and CCI evaluable participants in total, the numbers of participants in the 2 age groups will fall between a combination of CCI to a combination of CCI. With sample sizes of CCI and CCI in an age group, the power to show that the CCI% CI of the AUC_{0-12} geometric mean falls within the acceptance range (CCI to CCI-fold of the SPRINT AUC_{0-12} geometric mean; FDA Guidance 2014) will be 90%, 99.9% and > 99.9%, respectively. The power for two age groups falling within the acceptance range simultaneously will therefore be 90% × 99.9% ≈ 90% and 99.9% × 99.9% ≈ 99.9% for the CCI combination and CCI combination, respectively. This sample size calculation assumes that there is a ±CCI% difference in exposure between the granule and capsule formulation and assumes an inter-subject gCV% of CCI% (Wang et al 2012). The choice of gCV% is based on observations from Study 89 CCI%) and the SPRINT study (CCI%).

In the dose-finding phase of this study, the exposure AUC0-12 will be monitored on an ongoing basis. The minimum sample size for each cohort and the study may be re-estimated when CCI evaluable participants in that cohort have provided acceptable PK exposures. The re-estimation will use the observed inter-subject gCV%. Table 1 below shows the minimum sample sizes required in each age group corresponding to different variability and different scenarios.

Table 1 Sample Size Estimations based on Inter-subject gCV% and Expected Differences in AUC0-12 between SPRINKLE and SPRINT studies

Inter-subject gCV%	Difference in AUC0-12 between SPRINKLE and SPRINT studies		
	± 5%	± 10%	± 15%
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI
CCI	CCI	CCI	CCI

AUC $_{0\text{-}12}$, area under the concentration-time curve from time zero to 12 hours; gCV, geometric coefficient of variation.

Japan Cohort

In addition to the Global Cohorts (Cohorts 1 and 2), a separate Japan Cohort of a minimum of CCI evaluable participants aged ≥ 1 to < 7 years will be recruited.

Primary PK Analysis

During the dose-finding period the individual and median AUC0-12 derived from the Global Cohorts of participants given the granule formulation will be compared to the AUC0-12 CCI CCI percentile observed in the SPRINT study at CCI mg/m^2. If the dose is adjusted, then the AUC will be re-assessed at the adjusted dose to confirm with additional participants that exposure is within the CCI percentile of SPRINT exposure.

At the final sample size for the recommended dose schema in the Global Cohorts (Cohorts 1 and 2), the AUC0-12 geometric mean and CCI% CI will be determined for each age group and overall. If the CCI% CI falls within CCI % of the geometric mean AUC0-12 observed in the pivotal safety and efficacy study, SPRINT, then it will be considered that comparable exposure to selumetinib was observed across the age groups.

Box and whisker plots of observed AUC0-12 (and other PK parameters) will be produced for comparison to the target range for the capsule formulation determined from SPRINT.

Analysis Sets

- All enrolled set: all participants who sign the ICF.

- Pharmacokinetic analysis set: all participants who receive at least one dose of selumetinib and who have at least one post dose quantifiable plasma concentration with no important protocol deviations.
- Safety analysis set: all participants who receive at least one dose of selumetinib.

Note: The PK data for the Japan Cohort will be summarised separately from the PK data for the Global Cohorts.

There will be three analysis time points:

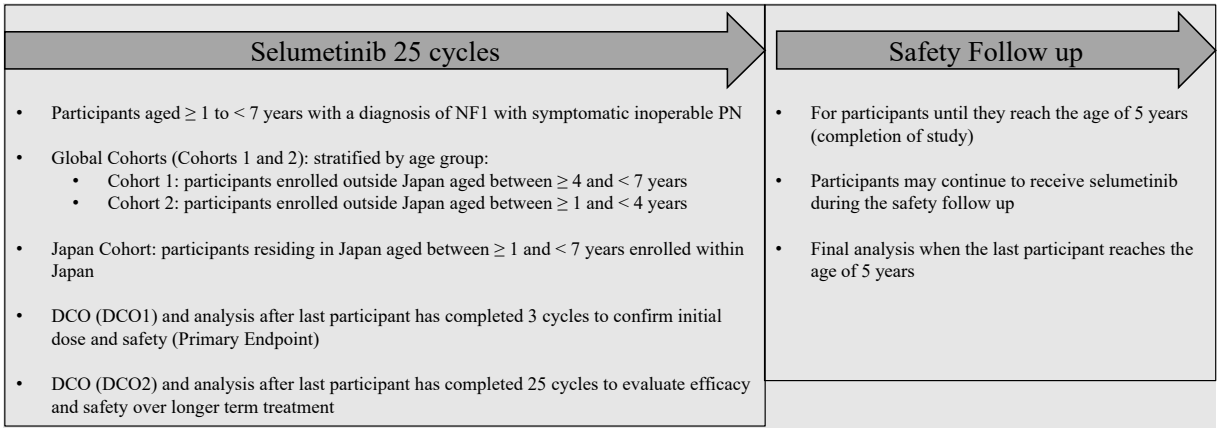
1 Pharmacokinetics, dose-finding and primary safety analysis: A DCO (DCO1) and analysis will occur after all participants have had the opportunity to complete 3 cycles of treatment. This primary analysis will confirm the recommended granule formulation dose schema and assess PK, safety/tolerability, and palatability. The timing of DCO1 may be different for the Global Cohorts (Cohorts 1 and 2) from the Japan Cohort, based on their date of Last Subject In.

2 Safety and efficacy of the granule formulation: A DCO (DCO2) and analysis will occur after all participants in the study (Global and Japan Cohorts) have had the opportunity to complete 25 cycles (or terminated selumetinib); this analysis will provide additional PK and safety/tolerability data, as well as palatability and efficacy data.

3 Long term safety follow-up for participants until they reach the age of 5 years or commence an alternative systemic NF1-PN treatment, whichever is the earlier: A final analysis will occur when all participants in the study (Global and Japan Cohorts) have had the opportunity to complete their last assessment in the study, including the safety follow-up for participants aged < 5 years.

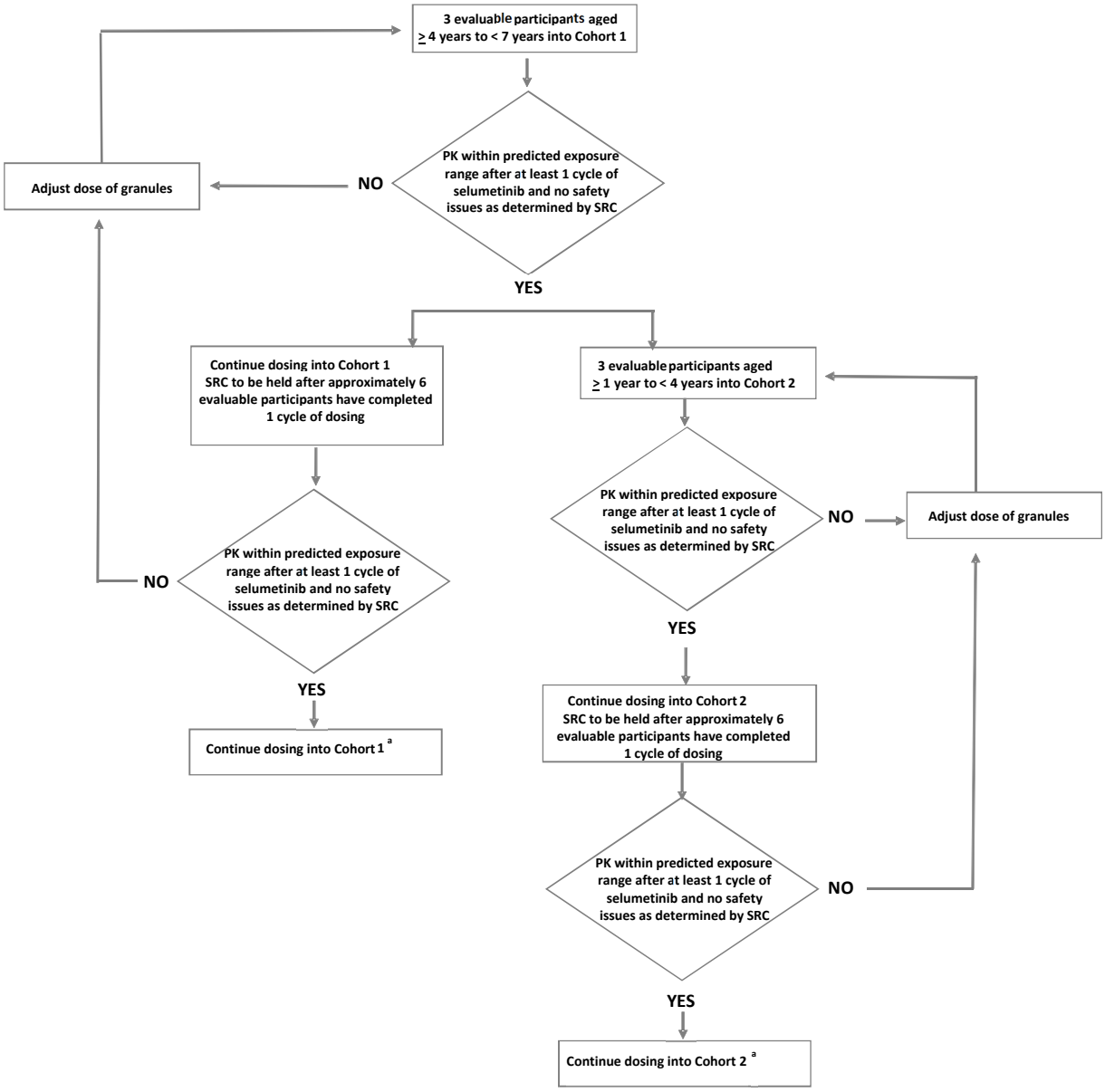
1.2 Schema

Figure 1 Study Design



DCO, data cut-off; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma.

Figure 2 Dose-finding Phase



a. Additional SRC to be held after approximately 10 evaluable participants have completed one cycle of dosing to re-evaluate sample size required for the cohort at the recommended granule formulation dose schema.

PK, pharmacokinetics; SRC, Safety Review Committee.

1.3 Schedule of Activities

Table 2 Schedule of Activities

Procedure	Screen	Intervention Period in Cycles (28-day cycle) [a]															EoT Safety Follow-up (30 days after last dose)	Section or Appendix
		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C7 D1	C9 D1	C11 D1	C13 D1	C17 D1	C19 D1	C21 D1	C25 D1	Day 7 after transition to capsule formulation [b]	EoT [c]		
Weeks		**1**	**3**	**5**	**9**	**13**	**17**	**25**	**33**	**41**	**49**	**65**	**73**	**81**	**97**				
Window (days)	**-28 to -1**	**0**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 3**	**± 3**	**+ 4 to 14**	**+ 7**	**+ 7**	
Informed consent [z]	X																		A 3
Inclusion and exclusion criteria	X																		5.1, 5.2
Demography	X																		5.1, 5.2
Full Physical examination including standard neurological examination	X			X	X	X	X	X	X	X	X	X		X	X		X	X	8.3.1
Abbreviated physical examination		X	X																8.3.1
Height, weight	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	8.3.2
BSA [d]	X	X		X	X	X	X	X	X	X	X	X		X	X	X			8.3.2
Disease characteristics [e]	X																		
Medical history	X																		5.1, 5.2

Table 2 Schedule of Activities

Procedure	Screen	Intervention Period in Cycles (28-day cycle) [a]															EoT Safety Follow-up (30 days after last dose)	Section or Appendix
		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C7 D1	C9 D1	C11 D1	C13 D1	C17 D1	C19 D1	C21 D1	C25 D1	Day 7 after transition to capsule formulation [b]	EoT [c]		
Weeks		**1**	**3**	**5**	**9**	**13**	**17**	**25**	**33**	**41**	**49**	**65**	**73**	**81**	**97**				
Window (days)	**-28 to -1**	**0**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 3**	**± 3**	**+ 4 to 14**	**+ 7**	**+ 7**	
Clinical safety lab assessments [f]	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	8.3.9
12-lead ECG	X			X			X		X		X	X		X	X		X	X	8.3.4
Echocardiogram [g]	X			X			X		X		X	X		X	X		X [g]	X [g]	8.3.5
Ophthalmology examination [h]	X			X			X		X		X			X			X	X [h]	8.3.6
Knee MRI/X-ray (Physeal dysplasia) [i]	X										X				X				8.3.7
Performance status [f]	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	8.3.8
Urinalysis [f]	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	8.3.9
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	8.3.3
PN assessments using volumetric MRI [j]	X						X		X		X		X		X		As per SoC [j]		8.2.1

Table 2 Schedule of Activities

Procedure	Screen	Intervention Period in Cycles (28-day cycle) [a]															EoT Safety Follow-up (30 days after last dose)	Section or Appendix
		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C7 D1	C9 D1	C11 D1	C13 D1	C17 D1	C19 D1	C21 D1	C25 D1	Day 7 after transition to capsule formulation [b]	EoT [c]		
Weeks		1	3	5	9	13	17	25	33	41	49	65	73	81	97				
Window (days)	-28 to -1	0	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 3	± 3	+ 4 to 14	+ 7	+ 7	

CCI

Table 2 Schedule of Activities

Procedure	Screen	Intervention Period in Cycles (28-day cycle) [a]															EoT Safety Follow-up (30 days after last dose)	Section or Appendix
		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C7 D1	C9 D1	C11 D1	C13 D1	C17 D1	C19 D1	C21 D1	C25 D1	Day 7 after transition to capsule formulation [b]	EoT [c]		
Weeks		**1**	**3**	**5**	**9**	**13**	**17**	**25**	**33**	**41**	**49**	**65**	**73**	**81**	**97**				
Window (days)	**-28 to -1**	**0**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 3**	**± 3**	**+ 4 to 14**	**+ 7**	**+ 7**	
CCI [redacted]																			
Palatability (Observer Palatability) [s]		Twice daily C1W1						Twice daily C7W1											8.2.7.6
Dispense medication [t]		X		X	X	X	X	X	X	X	X	X	X	X	X				6
Return medication/compliance check				X	X	X	X	X	X	X	X	X	X	X	X		X		6.2 6.4
Dispense/return ePRO device/review ePROs	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X		6.4
Daily Drug Diary		←═══ twice daily ═══→																	6.4
Review Daily Drug Diary			X	X	X	X	X	X	X	X	X	X		X	X	X	X		6.4
Blood for PD Biomarkers [u]		X																	8.6.2

Table 2 Schedule of Activities

Procedure	Screen	Intervention Period in Cycles (28-day cycle) [a]															EoT Safety Follow-up (30 days after last dose)	Section or Appendix
		C1 D1	C1 D15	C2 D1	C3 D1	C4 D1	C5 D1	C7 D1	C9 D1	C11 D1	C13 D1	C17 D1	C19 D1	C21 D1	C25 D1	Day 7 after transition to capsule formulation [b]	EoT [c]		
Weeks		**1**	**3**	**5**	**9**	**13**	**17**	**25**	**33**	**41**	**49**	**65**	**73**	**81**	**97**				
Window (days)	**-28 to -1**	**0**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**	**± 3**	**± 3**	**+ 4 to 14**	**+ 7**	**+ 7**	
PK blood samples [v, w]		X		X			X				X				X	X			8.6.1.1
Adverse Events [x]	X	←═══															→═══	X	8.4
Concomitant medication/ procedures	X	←═══															→═══	X	6.5
NF1 treatments [y]			←═══ collect for participants who discontinue selumetinib prior to C25 ═══→																

a. After 25 cycles (or discontinuation of selumetinib) participants who are aged < 5 years will enter a long term safety follow-up and assessments will be performed as per Table 3. After 25 cycles of treatment if participants are > 5 years of age and unable to access commercial supply and are still receiving clinical benefit participants may be able to remain on treatment in the study. Assessments will revert to standard of care at the particular site. There will be no more data collection except SAE, overdose and pregnancy reporting. All SAEs, overdoses and pregnancies will be reported until 30 days after last dose.

b. Once participants attain a BSA between 1.10 and 1.29 m^2 they will be encouraged to completely transition to the capsule formulation, if feasible, although all participants must remain on the granule formulation until after they have completed their third cycle of treatment.

c. An EoT visit will be performed for participants who permanently discontinue study intervention for any reason (except for death, lost to follow-up, or withdrawal of consent). The EoT visit should be performed as soon as possible after the end of treatment.

d. Calculation of BSA should be done at the specified time points but since BSA determines the dose of selumetinib it should also be calculated more frequently, as appropriate, depending on the age and growth rate of the child.

e. Assessment of baseline disease characteristics includes documenting location of the target and non-target PN (if applicable), any PN-related symptoms and results of any previous genetic testing for NF1. (Participants recruited under CSP Version 1.0 will have this data entered in the EDC if available retrospectively.)

f. If clinical safety laboratory assessments, urinalysis and performance status have been done within 14 days of starting study intervention they do not need to be repeated on C1D1 if the participant's condition has not changed. If laboratory procedures were performed for alternate reasons prior to signing consent (but within the 28 day screening window), these can be used for screening purposes with consent of the legally authorised representative (parent or guardian) of the participant.

g. The participant should be examined using the same machine and operator throughout the study wherever possible with a ± 7 day window for each assessment. If a participant has had an echocardiogram performed within 4 weeks prior to treatment discontinuation, the EoT visit echocardiogram scan is not required unless clinically indicated. An echocardiogram should be performed at the 30 day safety FU only in participants who have a drop in LVEF of ≥ 10 percentage points from baseline and to below the LLN at the time of selumetinib end of treatment visit, or if clinically indicated. Participants who have a drop in LVEF of >10 percentage points from baseline and to below the LLN at the time of selumetinib discontinuation should have a follow-up ECHO, ECG, vital signs and weight performed at 30 day safety follow-up.

h. Assessment window ± 7 days. Ophthalmologic assessments may be performed more often, if clinically indicated, please see Appendix E 3 for more information. An ophthalmological examination should be performed at the 30 day safety FU only in participants with a retinal abnormality prior to or at time of end of treatment visit.

i. Where feasible the knee MRI/X-ray will be performed at the same time as the PN volumetric MRI with a ± 7 day window for each assessment. Note that a wrist MRI/X-ray is acceptable if it is not possible to perform knee MRI/X-ray. The joint, which is imaged must be consistent throughout the study, except occasions where MRI/X-ray of the joint imaged at baseline is not possible.

j. Plexiform neurofibroma assessments will be performed at screening and every 4 cycles (16 ± 1 weeks) for the first 13 cycles, and subsequently every 6 cycles (24 ± 1 weeks). MRI data for participants who discontinue selumetinib prior to C25 will be collected if a suitable MRI is performed as part of SoC until the time when they would have completed 25 cycles of treatment, or they commence an alternative systemic NF1-PN treatment, whichever is the

CCI

Twice daily for Cycle 1, Week 1 and Cycle 7, Week 1. If the assessment cannot be done at Cycle 7, Week 1 then it should be performed as soon as possible afterwards. The Cycle 7, Week 1 assessments should not be completed if the participants are receiving selumetinib capsules. Additional optional assessments of palatability can be performed for 7 days when a participant changes doses due to a change in BSA.

t. Selumetinib will be dispensed every cycle (every 28 days ± 3 days) until Cycle 13, and subsequently every other cycle (± 3 days). If feasible, site to participant transport of study drug will be utilised.

u. Samples for pERK inhibition should only be taken in participants weighing ≥ 27 kg. Samples should be taken pre-dose within 10 minutes prior to dosing, at 1 and 3 hours post-dose (± 15 minutes), and at 18-24 hours post-dose.

v. Blood samples to measure selumetinib and N-desmethyl selumetinib metabolite will be collected pre-dose within 10 minutes prior to dosing, and 1, 2, 3, and 4 hours post-dose ± 15 minutes; 6 and 8 hours post-dose ± 30 minutes; 10-12, and 18-24 hours after selumetinib single dose on Cycle 1, Day 1 (only 1 dose will be given on Cycle 1, Day 1); bid continuous dosing will start from Cycle 1, Day 2 and blood samples will be taken pre-dose, 1, 2, 3, 4, 6, 8, and 10-12 hours post-dose on Cycle 2, Day 1. The Cycle 2, Day 1 12 hour sample should be taken prior to the second dose. At any other visit (as indicated in the table), only pre-dose blood sample will be collected. In participants that transition from granule formulation to capsule formulation, blood samples will be taken on Day 7 (range Day 4 to 14) pre-dose, 0.5, 1.5, 3, 6, and 10-12 hours post-dose, as long as the participant has received 3 consecutive days of twice daily dosing with capsule formulation immediately prior to the PK day.

w. For operational reasons, the pharmacokinetic sampling on Cycle 2, Day 1 can take place on any day between Cycle 1, Day 24 and Cycle 2, Day 8 as long as the participant has received 3 consecutive days of bid dosing immediately prior to the PK day. Every effort should be made to conduct PK sampling within the window. However, if for unforeseen reasons this is not possible, PK sampling can be performed at any time from 7 days prior to Cycle 2, Day 1 to the end of cycle 3 provided the participant has received 3 consecutive days of dosing immediately prior to the PK day.

x. Adverse events will be collected from the time of signing the informed consent form, throughout the treatment period, and including the follow-up period.

y. Other systemic NF1-PN targeted treatments will be collected for all participants who discontinue selumetinib until the time when they would have completed 25 cycles of treatment, or they commence an alternative systemic NF1-PN treatment whichever is the earliest.

z. Consent can be performed on Day -42 onwards. All screening assessments must be performed within 28 days prior to dosing.

CCI [redacted]; BSA, body surface area; C, cycle; CSP, Clinical Study Protocol; D, day; CCI [redacted]; ECG, electrocardiogram; EDC, electronic data capture; EoT, end of treatment; CCI [redacted]; FU, follow-up; CCI [redacted] LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; PD, pharmacodynamic; CCI [redacted]; PK, pharmacokinetic(s); PN, plexiform neurofibroma; SoC, standard of care; VMI, Visual-Motor Integration; W, week.

Table 3 Schedule of Activities – Safety Follow-up until Participants are aged 5 Years

	Participants receiving selumetinib treatment [a]			Participants no longer receiving selumetinib treatment		
Procedure [b]	**Every 6 cycles**	**Every 12 cycles**	**EoT Safety Follow-up (30 days after last dose)**	**Every 6 months**	**Every year**	**Section or Appendix**
Window	**± 7 days**	**± 7 days**	**+ 7 days**	**± 7 days**	**± 7 days**	
Full Physical examination	X		X	X		8.3.1
Height, weight	X		X	X		8.3.2
BSA	X			X		8.3.2
Clinical safety laboratory assessments	X		X	X		8.3.9
12-lead ECG	X		X	If clinically indicated		8.3.4
Echocardiogram	Approximately every 3 cycles		X	If clinically indicated		8.3.5
Ophthalmology examination		X	X	If clinically indicated		8.3.6
Knee MRI/X-ray (Physeal dysplasia)		X			X	8.3.7
Performance status	X		X	X		8.3.8
Urinalysis	X		X	X		8.3.9
Vital signs	X		X	X		8.3.3
CCI [redacted]						
Dispense medication [d]	To be dispensed every 2 cycles					6
Return Medication/Compliance Check	←==========→		X			6.2 6.4
SAEs and AEs causally related to selumetinib	←==========→		X	←==========→		8.4

a. PN tumour assessment should be continued as standard of care if participants remain on treatment. No information about the MRI will be collected (i.e., not date/time of scan or images).

b. The participant should continue to attend all assessments as described until they are ≥ 5 years of age (assessments should continue until the first visit after their 5th birthday) or commence an alternative systemic NF1-PN targeted treatment, whichever is earlier.

CCI [redacted]

Selumetinib will be dispensed every 2 cycles (± 3 days). If feasible, site to participant transport of study drug will be utilised.

AE, adverse event; BSA, body surface area; ECG, electrocardiogram; EoT, end of treatment; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; PN, plexiform neurofibroma; SAE, serious adverse event.

2 INTRODUCTION

2.1 Study Rationale

Selumetinib capsule is approved by the FDA for the treatment of paediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN and a Conditional Marketing Authorisation was granted in Europe/EEA for paediatric patients 3 years of age and older, via the European Centralised Procedure on 17 June 2021. The efficacy of selumetinib in the treatment of NF1-related inoperable PN in paediatric participants was demonstrated in the SPRINT study; safety data from this study showed that selumetinib has a manageable safety profile with favourable tolerability over several years of treatment in this population.

Selumetinib is currently available in a capsule formulation which precludes administration to children with a BSA of < 0.55 m^2 or very young children who may have difficulty swallowing capsules. Therefore, AstraZeneca has developed an alternative age appropriate granule formulation of selumetinib for infants and young children aged ≥ 1 to < 7 years which is contained within a sprinkle capsule.

The relative bioavailability of the granule and capsule formulations has been investigated in adult healthy male subjects (Study D1532C00089, Study 89); with a geometric mean ratio (90% CI) of 0.654 (0.581, 0.736) for dose-normalized Cmax and 0.865 (0.811, 0.922) for dose-normalized AUC. The selumetinib content in the granule formulation batch used in Study 89 was CCI % therefore, when corrected for selumetinib content, the granule AUC was only CCI % lower compared to capsule. The selumetinib content in the granule formulation which will be used in the SPRINKLE study will be approximately CCI %.

This study is designed to define a dosing regimen and assess the PK and safety of the granule formulation; the study will also include descriptive analyses of the exploratory efficacy endpoints. Assuming that the AUC in this study is similar to the AUC observed in SPRINT, efficacy in children aged ≥ 1 to < 7 years can be extrapolated from the SPRINT study (Gross et al 2020). The study will inform the benefit risk profile of the granule formulation in children aged ≥ 1 to < 7 years with NF1-related symptomatic, inoperable PN.

2.2 Background

Neurofibromatosis type 1 is an autosomal dominant disorder with an estimated prevalence of 2.13/10,000 individuals in Europe (OrphaNet Report Services 2020). There are no studies estimating the prevalence of NF1 in the US and most authors cite studies conducted in Europe. Neurofibromatosis type 1 is characterised by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations. Symptoms of NF1 generally manifest very early in life and the subsequent increase in morbidity can be severe.

Neurofibromatosis type 1 arises from pathogenic variants of the NF1 gene encoding the

tumour suppressor protein neurofibromin, a GTPase-activating protein whose normal function is to downregulate RAS activity (Ballester et al 1990, Bollag and McCormick 1991, Cawthon et al 1990, Martin et al 1990, Viskochil et al 1990, Wallace et al 1990). Constitutive activation of the RAS/RAF/MEK/ERK pathway is implicated in cell proliferation and is central to driving cancer growth and progression (Davies et al 2007). Neurofibromin 1 pathogenic variants lead to a failure to inactivate RAS, and can result in PNs (Basu et al 1992, Cichowski et al 2003). 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 (Gutmann et al 2013, Ruggieri and Packer 2001).

Plexiform neurofibromas develop in 20% to 50% of individuals with NF1. Plexiform neurofibromas in NF1 patients are histologically benign Schwann-cell tumours (Rutkowski et al 2000, Wu et al 2005) that, depending on the location and the growth rate, bear all the characteristics typical of cancers. 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). Growth of PNs occurs more rapidly in young children (Akshintala et al 2020, Nguyen et al 2012, Tucker et al 2009). Spontaneous regression of PNs is uncommon and although occasionally seen in adolescents and young adults, it was not seen in young children (Akshintala et al 2020, Gross et al 2018). Consequently, there is a significant treatment need for young children with NF1-PN. These tumours can cause severe morbidity such as pain, neurological dysfunction, and disfigurement, and also have the potential to transform to 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); MPNST is a rare disease in the general population with a lifetime incidence of 0.001% (Ferrari et al 2007).

Selumetinib (AZD6244, ARRY 142886, AR00142886, AR-142886-X [where X refers to a sequential lot number], KOSELUGO®) is an oral, potent, and highly selective, allosteric MEK1/2 inhibitor with a short half-life (Banerji et al 2010, Denton and Gustafson 2011). It is licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma and is being co-developed by AstraZeneca and Merck & Co. Selumetinib can inhibit PN growth by blocking RAS signalling (Gross et al 2018, Gross et al 2020, Weiss et al 1999, Widemann et al 2014).

Analysis of volumetric MRI data by NCI POB central review from a Phase I open-label, single-arm, Investigator-sponsored study (Study 8799 [NCI 11-C-0161; SPRINT; NCT01362803]) in paediatric patients (aged 3 to 18 years at enrolment) with NF1-related inoperable PN demonstrated durable tumour shrinkage with confirmed tumour volume decreases of ≥ 20% from baseline (Dombi et al 2016). These observations led to the addition

of a Phase II part to the study to further evaluate the effect of selumetinib capsules on tumour response, pain, quality of life, and physical functioning in paediatric patients (aged 2 to 18 years at enrolment) with NF1-related symptomatic inoperable PN. Analysis of volumetric MRI data by NCI POB central review from SPRINT Phase II Stratum 1 showed durable tumour shrinkage along with clinical benefit (Gross et al 2020).

The NCI POB central analysis-assessed ORR was 66% (95% CI: 51.2 to 78.8) in the SPRINT study. The median time to onset of response was 7.2 months (range 3.3 months to 1.6 years). The median DoR from onset of response was not reached; at the time of DCO the median follow-up time was 22.1 months. Of the 33 patients who had confirmed PR, 27 (81.8%) remained in response after 12 months; the remaining 6 patients were censored and had not progressed. The median time from treatment initiation to disease progression while on treatment was not reached. At the time of DCO, 28 (56%) patients remained in confirmed PR, 2 (4%) had unconfirmed PRs, 15 (30%) had stable disease and 3 (6%) had PD.

Clinical Outcome Assessments were generally improved with an overall reduction in pain, improvement in motor function and mobility, improved bowel and bladder function and overall improvement in quality of life assessments. Selumetinib showed good tolerability with mainly mild or moderate AEs which were manageable long term via supportive therapy and/or dose interruption or reduction.

The safety, tolerability, PK, and efficacy of selumetinib capsules in Japanese paediatric patients with NF1 and inoperable and symptomatic PNs is being investigated in the Phase I Study D1346C00013 (NCT04495127). An interim data cut-off (DCO1 on 16 June 2021) after all 12 patients had reached Cycle 7 Day 1 demonstrated that selumetinib capsule monotherapy is well tolerated and has a manageable safety profile in paediatric Japanese patients with NF1-related PN. Additionally, the PK profile of selumetinib capsules in Japanese paediatric patients appeared to be similar to that observed in the pivotal SPRINT study. Following a single 25 mg/m^2, selumetinib geometric mean ratio (90% CI) for Cmax and AUC0-12 were 1.07 (0.79, 1.45) and 1.26 (1.02, 1.55), respectively, for Study 13 compared to SPRINT Phase II Stratum 1. Given the considerable overlap of these exposures and that there was no clear relationship observed for exposure and safety or efficacy, these differences are not considered clinically relevant. There is no dose adjustment required for Japanese patients; the recommended dose is [redacted] mg/m^2.

Selumetinib (KOSELUGO®) capsules were approved for the treatment of paediatric patients ≥ 2 years of age with NF1 who have symptomatic, inoperable PN in the US on 10 April 2020 and a Conditional Marketing Authorisation was granted in Europe/EEA for paediatric patients 3 years of age and older, via the European Centralised Procedure in the EU on 17 June 2021.

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

2.3 Benefit/Risk Assessment

More detailed information about the known and expected benefits and potential risks of selumetinib may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

The potential risks associated with selumetinib or with the study procedures are shown in Table 4. Guidance and algorithms for the management of these risks are described in Appendix E.

Table 4 Risk Assessment

Potential risk of clinical significance	Rationale for risk	Mitigation strategy
Potential risks associated with selumetinib		
Gastrointestinal effects: diarrhoea, nausea and vomiting	Diarrhoea, nausea and vomiting are reported very commonly, mostly Grade 1 or 2 but with some Grade 3 events. SAEs of diarrhoea have been reported. In very young children, early intervention may be required to prevent dehydration.	Dose interruptions or modifications to the selumetinib dose. See Appendix E for management guidelines for diarrhoea.
Vision blurred Central Serous Retinopathy Retinal Pigment Endothelial Detachment Retinal vein occlusion	Blurred vision (Grade 1 or 2) is a common ADR and may indicate the early onset of a more serious underlying retinal toxicity, although RVO, CSR and RPED have not been seen in paediatric patients in the pivotal study. In young children, communication of visual disturbance may be difficult, making early detection and mitigation more challenging.	Exclusion of participants with: current or past history of CSR; history of RVO; IOP > 21 mmHg; or uncontrolled glaucoma (irrespective of IOP). An ophthalmologic examination will be evaluated at the times outlined in the SoA, and as clinically indicated. See Appendix E for management guidelines.
Creatine phosphokinase increase	CPK increase is a very commonly reported ADR in paediatric patients. In paediatric patients, elevated CPK reports have all been asymptomatic, largely Grade 1 or 2 but some Grade 3 events and SAEs have been reported. Although myopathy directly associated with CPK elevation, or rhabdomyolysis have not been reported in paediatric patients, this is a class effect. Detection and management of elevated CPK levels are therefore considered important risk mitigation.	Dose interruptions or modifications to the selumetinib dose. See Appendix E for management guidelines.
Rash/dermatitis acneiform.	Rash and dermatitis acneiform are very commonly reported ADRs in paediatric patients. The majority are Grade 1 or 2 but some Grade 3 events have been reported. Dermatitis acneiform has predominantly been reported in post-pubertal children. In paediatric patients rash was not considered to be associated with skin infection/cellulitis but management according to toxicity management guidelines is considered important to improve tolerability.	Dose interruptions or modifications to the selumetinib dose. See Appendix E for management guidelines.

Table 4 Risk Assessment

Potential risk of clinical significance	Rationale for risk	Mitigation strategy
Left ventricular ejection fraction decreases	Asymptomatic, Grade 1 or 2 LVEF decrease identified on routine ECHO are reported as very common ADRs in paediatric patients. Although symptomatic LVSD has not been reported in paediatrics, routine ECHO is important to detect any abnormality especially in very young patients for whom detection of symptoms (eg, dyspnoea, oedema, fatigue) may be more challenging.	Exclusion of participants with current unstable or uncompensated cardiac conditions or LVEF below LLN. See Appendix E for management guidelines.
Physeal dysplasia	Growth plate abnormalities have been seen in a single animal species at 11 times the clinical free exposure. This finding has also been reported preclinically with other MEK inhibitors. This preclinical risk has not been identified clinically following longitudinal assessment of height and growth velocity in paediatric patients on selumetinib (median total duration of exposure 28.1 months). However, there remains a potential risk of physeal dysplasia in paediatric patients with open growth plates, which could lead to joint pain and limb shortening. Routine monitoring during clinical studies is therefore required.	The healthcare professionals involved in clinical studies on paediatric populations should look for signs of physeal dysplasia (eg, joint pain and fatigue after exercising, abnormal gait, spine irregularities). Children who show signs of physeal dysplasia during treatment may need assessment of the knee or wrist joint by X-ray or MRI to assess for physical dysplasia. If clinical symptoms are identified at the time of selumetinib discontinuation participants should have a follow-up assessment after 30 days to evaluate the potential for reversibility.

ADR, adverse drug reaction; CPK, creatine phosphokinase; CSR, central serous retinopathy; ECHO, echocardiogram; IOP, intraocular pressure; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; MEK, mitogen activated protein kinase; MRI, magnetic resonance imaging; RPED, retinal pigment endothelial detachment; RVO, retinal vein occlusion; SAE, serious adverse event; SoA, schedule of activities.

2.3.2 Benefit Assessment

Selumetinib capsules have been shown to be effective in the treatment of paediatric patients with NF1 who have symptomatic, inoperable PN and are approved in the US for the treatment of paediatric patients aged ≥ 2 years of age. In the pivotal SPRINT study, selumetinib showed a durable and sustained tumour shrinkage, with an overall response rate of 66%, alongside improvement in clinical outcomes (Gross et al 2020). There are no other approved treatments for NF1-PN. It has been demonstrated previously that younger NF1-PN patients have faster growing PNs (Akshintala et al 2020, Nguyen et al 2012, Tucker et al 2009). An analysis of patient response to selumetinib treatment in the SPRINT study by age group shows that there is a numerically higher ORR in the youngest age group (≥ 3 to 7 years), although benefit was observed in all ages. Therefore, it is likely that the participants in this study might derive clinical benefit from treatment with the granule formulation of selumetinib.

As shown from the relative bioavailability study (D1532C00089; Study 89), food is not expected to affect the primary PK analysis variable AUC. Without the fasting restrictions, it is intended that the granule formulation dosing posology will be more convenient and pragmatic for this younger patient group.

Participants in the study may therefore benefit from treatment. Following the end of the study, a mechanism will be in place to ensure that participants will be able to continue taking selumetinib as long as they derive clinical benefit, as judged by the investigator.

2.3.3 Overall Benefit: Risk Conclusion

The investigation of selumetinib in participants with NF1-related symptomatic, inoperable PN appears favourable based upon: the non-clinical safety profile, the available clinical efficacy and safety profile, the risk minimisation, and AE management proposals including manageability of various toxicities and the lack of effective alternative treatments.

During SPRINT it has been established that the safety profile of selumetinib is reflective of its pharmacological action, with adverse drug reactions that are both monitorable and manageable. The majority are mild or moderate in severity, and in many cases resolve without dose modification. However, where required, dose interruptions and/or in some cases a dose reduction have shown that symptoms are reversible. Serious adverse events and treatment discontinuations due to AEs are low.

Since the young participants in this study may not be able to self-report any toxicities, close monitoring has been put in place to ensure early detection of any potential risks.

Overall, the benefit/risk assessment supports the administration of selumetinib to participants with NF1-related symptomatic, inoperable PN.

3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints of the study are shown in Table 5.

Table 5 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the PK of selumetinib after administration of the selumetinib granule formulation.	• Selumetinib AUC0-12 derived after single dose administration.
• To assess the safety and tolerability of the selumetinib granule formulation.	• Safety and tolerability will be evaluated in terms of AEs, clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis), physical examination, weight, vital signs, ECG, ECHO, ophthalmologic assessment, knee (or wrist) MRI/X-ray, and performance status. • Assessments related to AEs will include: occurrence/frequency; relationship to study intervention; CTCAE grade; seriousness; death; AEs leading to discontinuation of study intervention; AEs of special interest.
Secondary	
• To assess the palatability of the selumetinib granule formulation	• Palatability will be assessed using the parent-reported observer palatability assessment.
• To further assess the PK of selumetinib and N-desmethyl selumetinib metabolite after administration of the selumetinib granule formulation.	• Plasma concentrations and PK parameters of selumetinib including, but not limited to: ◦ Selumetinib AUC0-12 derived after multiple dose administration. ◦ Cmax, AUC0-6, AUClast, CL/F, tmax, tlast derived after single and multiple dose administration. ◦ AUC0-24, Vz/F and t½λz after single dose administration. ◦ Rac Cmax, Rac AUC0-12, and Vss/F derived after multiple dose administration. • Plasma concentrations and PK parameters of N-desmethyl selumetinib including, but not limited to: ◦ Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after single and multiple dose administration. ◦ Rac Cmax and Rac AUC0-12 derived after multiple dose administration. • Parent-to-metabolite ratio for AUC0-6, AUC0-12 and AUC0-24 (single dose only), and Cmax after single and multiple dose administration.
• To evaluate the efficacy of the selumetinib granule formulation by assessment of ORR as determined by ICR per REiNS criteria.	• Objective Response Rate

Table 5 Objectives and Endpoints

Objectives	Endpoints
Exploratory Objectives	
• To evaluate the efficacy of the selumetinib granule formulation by assessment of CCI as determined by ICR per REiNS criteria.	• CCI • CCI • CCI • CCI
• To evaluate efficacy of the selumetinib granule formulation by assessment of CCI	• Parent-reported CCI total score.
• To evaluate efficacy of the selumetinib granule formulation by assessment of CCI .	• CCI
• To evaluate the safety of the selumetinib granule formulation by assessment of CCI	• CCI to assess language, motor skills and cognitive functions in participants aged < 3.5 years. • CCI to assess language and cognitive functions in participants aged ≥ 3.5 years. • CCI to assess motor skills in participants aged ≥ 3.5 years. • CCI .
• To evaluate the pharmacodynamic effect of selumetinib in PBMCs.	• Change from baseline in PD markers which may include but may not be limited to pERK

• To determine the PK of selumetinib and N-desmethyl selumetinib after administration of the selumetinib capsule formulation.	• Plasma concentrations and PK parameters of selumetinib including, but not limited to:
	  ° Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after multiple dose administration.
	  ° CL/F and VssF derived after multiple dose administration.
	• Plasma concentrations and PK parameters of N-desmethyl selumetinib including, but not limited to:
	  ° Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after multiple dose administration.
	  ° Parent to metabolite ratio for AUC0-6, AUC0-12, and Cmax after multiple dose administration.
	• For the participants that transition to capsule formulation, CCI AUC0-6, AUC0-12, AUClast and Cmax will be determined following multiple dose administration of granule and capsule formulation. The ratio of granule:capsule formulation will be determined for each of these parameters.

Table 5 Objectives and Endpoints

Objectives	Endpoints
• CCI analyses will be completed to investigate the selumetinib exposure-response relationship for safety, biomarkers and efficacy.	• CCI analyses will be completed to assess the effect of CCI on selumetinib granule and capsule PK, including all paediatric PK data available. In addition, if data allows, CCI analyses will be completed to investigate the selumetinib exposure-response relationship for safety, biomarkers and efficacy.
• To explore potential biomarkers in residual PK or PD samples, which may influence the progression of neurofibromatosis and inoperable PNs (and associated clinical characteristics) and/or identify participants likely to respond to selumetinib or, may be surrogate markers of response.	• Exploratory biomarker analysis that may include (but not limited to) change from baseline in the expression and activity of neurofibromatosis and MEK pathways and/or specific RNA transcripts (arrays) as a surrogate for protein expression.

AE, adverse event; AUC, area under the concentration time curve; AUC0-6, area under the concentration-time curve from time zero to 6 hours; AUC0-12, area under the concentration-time curve from time zero to 12 hours; AUC0-24, area under the concentration-time curve from time zero to 24 hours; AUClast, area under the concentration-time curve from time zero to time of last measurable concentration; CCI CCI CL/F, apparent total clearance of the drug from plasma; Cmax, maximum peak plasma concentration; CTCAE, Common Terminology Criteria For Adverse Events; CCI , CCI ; ECG, electrocardiogram; ECHO, echocardiogram; CCI CCI CCI ICR, independent central review; MEK, mitogen-activated protein kinase; MRI, magnetic resonance imaging; ORR, objective response rate; PBMC, peripheral blood mononuclear cells; PD, pharmacodynamic; CCI ; PK, pharmacokinetics; PN, plexiform neurofibroma; Rac, relative accumulation ratio; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; RNA, ribonucleic acid; CCI t½λz, elimination half-life; tlast, time to last measurable concentration; tmax, time to maximum concentration; VssF, apparent volume of distribution at steady state after non-intravenous administration; Vz/F, apparent volume of distribution after non-intravenous administration.

4 STUDY DESIGN

4.1 Overall Design

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

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 GCP, and minimise 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 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 Medical Monitor.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- 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.

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

4.1.2 Overall Design

This is a Phase I/II, single-arm, open-label study in children aged ≥ 1 to < 7 years at study entry (date of ICF signature) with a clinical diagnosis of NF1-related symptomatic, inoperable PN. The

study is designed to evaluate the PK, safety and tolerability of selumetinib given as a granule formulation.

Participants will receive selumetinib for 25 cycles (or until they meet discontinuation criteria).

Enrolment into the Global Cohorts (Cohorts 1 and 2) will be stratified by age group:

- Cohort 1: participants enrolled outside Japan aged between ≥ 4 and < 7 years
- Cohort 2: participants enrolled outside Japan aged between ≥ 1 to < 4 years

After completion of at least one cycle (28 days) of dosing in 3 evaluable participants in Cohort 1, SRC will review the emerging safety and PK data. Providing the single dose PK exposure is within the acceptable range and there are no safety concerns as determined by SRC then dosing in Cohort 2 will be initiated and additional participants will be dosed in Cohort 1. If the PK exposure is not within the acceptable range, the dose may be adjusted to ensure that selumetinib exposure is within the range observed in the SPRINT study; PK will be assessed against acceptance criteria in an additional 3 evaluable cohort 1 participants who received the adjusted dose. Cohort 2 will be initiated once the selumetinib granule formulation dose schema is identified for Cohort 1. The physiologically-based PK model will be updated, if required, based on emerging PK data.

Additional SRC reviews will be held for each of the cohorts following at least one cycle of dosing in approximately 6 evaluable participants and again in approximately 10 evaluable participants. The SRC will evaluate the PK, safety and tolerability of the granule formulation for that dose schema. The Japan cohort will not participate in dose-finding phase. Further information on the SRC can be found in Section 9.6.In addition to the Global Cohorts, Japanese participants in Japan aged between ≥ 1 to < 7 years with NF1 related symptomatic, inoperable PN will be enrolled into the Japan Cohort.

At enrolment participants must have a BSA within the range 0.40 to 1.09 m^2; once participants attain a BSA between 1.10 and 1.29 m^2 they will be encouraged to transition to the capsule formulation, if feasible, although all participants must remain on the granule formulation until after they have completed their third cycle of treatment.

Participants who are aged ≥ 5 years at the end of 25 cycles of selumetinib will be considered to have completed the study for data analysis purposes. Participants who terminate treatment prior to Cycle 25 will be followed up to collect MRIs performed as standard of care, and details of NF1-PN treatment information until the time when they would have completed 25 cycles of treatment, or they commence an alternative systemic NF1-PN treatment, whichever is the earliest. Any participant who is aged < 5 years after 25 cycles of selumetinib (or when they terminate treatment with selumetinib) will enter a safety follow-up phase until they reach the age of 5 years or commence an alternative systemic NF1-PN treatment, whichever is the earlier. Participants can continue to receive selumetinib (capsule or granule formulations) during the safety follow-up as long as they are considered to be receiving benefit in the opinion of their Investigator. The safety follow-up is designed to assess long term safety of selumetinib treatment in participants who are < 3

years of age when they commence selumetinib as there are no long term safety data currently available for patients who received selumetinib at this age.

Continued Access to Study Intervention after the End of the Study

After the participant's last visit, AstraZeneca will continue to supply selumetinib to participants whilst they are still receiving clinical benefit as outlined in Section 6.7 or until meeting any other discontinuation criteria as defined in Section 7.1.

4.2 Scientific Rationale for Study Design

The efficacy of selumetinib capsule in the treatment of NF1-related symptomatic, inoperable PN in paediatric participants was demonstrated in the SPRINT study in which selumetinib was taken bid under fasted conditions (fast for 2 hours before each dose and one hour after each dose). Safety data from this study showed that selumetinib has a generally predictable and manageable safety profile in this population. Study D1346C00013 (NCT04495127) demonstrated selumetinib capsule monotherapy is well tolerated and has a manageable safety profile in all CCI paediatric Japanese patients with NF1-related PN, and that the PK profile appeared to be similar to that observed in the pivotal SPRINT study. Following a single CCI mg/m^2, selumetinib geometric mean ratio (90% CI) for Cmax and AUC0-12 were CCI and CCI respectively, for Study 13 compared to SPRINT Phase II Stratum 1. Given the considerable overlap of these exposures and that there was no clear relationship observed for exposure and safety or efficacy, these differences are not considered clinically relevant. There is no dose adjustment required for Japanese patients; the recommended dose is CCI mg/m^2.

Selumetinib is currently available in a capsule formulation which precludes administration to children with a BSA of < 0.55 m^2 or very young children who may have difficulty swallowing capsules. Therefore, AstraZeneca has developed an alternative age appropriate granule formulation of selumetinib for infants and young children aged ≥ 1 to < 7 years which is contained within a sprinkle capsule.

A relative bioavailability study (D1532C00089; Study 89) has been conducted in healthy adult volunteers with both selumetinib commercial capsule formulation and the granule formulation; both formulations were considered to have a similar extent of exposure (AUC) with a geometric mean ratio (90% CI) of 0.86 (0.81, 0.92). (AstraZeneca notes the selumetinib content for the granule formulation batch used in Study 89 was CCI% and would contribute to the lower exposure determined for the granule, whereas the selumetinib content in the current study is expected to be close to CCI%.) In addition, the effect of a low-fat meal on the granule formulation was investigated; no food effect was observed on the overall extent of exposure (AUC) with a geometric mean ratio (90% CI) of 0.97 (0.91, 1.02).

This study is designed to define a dosing regimen and assess the PK and safety of the granule formulation in children aged ≥ 1 to < 7 years with NF1-related symptomatic, inoperable PN; the study will also include descriptive analyses of exploratory efficacy endpoints. It is anticipated that efficacy in children aged ≥ 1 year can be extrapolated from the SPRINT study assuming that the

AUC for the granule formulation is similar to the AUC for the capsule formulation observed in SPRINT. The study will inform the benefit risk profile of the granule formulation in children aged ≥ 1 to < 7 years with NF1-related symptomatic, inoperable PN.

The safety measures chosen and the PK parameters to be assessed are standard for a Phase I/II study of this type.

4.3 Justification for Dose

The approved capsule dose of selumetinib for the treatment of NF1-related symptomatic, inoperable PN in paediatric patients 2 years of age and older is CCI mg/m^2 bid.

In this study the selumetinib granule formulation will be administered using BSA-based dosing. The modelling predictions suggest CCI mg bid for children with BSA of 0.40 to 0.49, 0.50 to 0.59, and 0.60 to 0.69 m^2, respectively, to achieve the equivalent exposure of up to CCI mg/m^2 bid in participants with BSA ≥ 0.70 m^2; the modelling accounts for possible age related changes in, for example, absorption and metabolism (CYP enzymes maturation processes) in children under 3 years old. For participants with a BSA 0.7 m^2 and above, dosing recommendations with the granule formulation are CCI with dosing recommendations for selumetinib commercial capsule formulation.

The initial proposed selumetinib granule formulation dose schema is based upon physiologically based PK simulations. Emerging PK data will be assessed and the selumetinib dose schema may be adjusted to ensure exposure to selumetinib is within the range observed in the SPRINT study (see Section 6.1.2). The physiologically-based PK model will be updated, if required, based on emerging PK data and the initial proposed dose schema may be adjusted.

4.4 End-of-Study Definition

For the purpose of Clinical Trial Transparency, the definition of the end of the study differs under FDA and EU regulatory requirements:

- European Union requirements define study completion as the last visit of the last participant for any protocol related activity.
- Food and Drug Administration requirements defines 2 completion dates:
  - Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.
  - Study Completion Date – is defined as the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including their last scheduled procedure at their last visit or contact.

The study may be stopped if, in the judgement of AstraZeneca, study participants are placed at undue risk because of clinically significant findings.

See Section 6.7 for details on participant management following the final DCO as well as following study completion.

5 STUDY POPULATION

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

5.1 Inclusion Criteria

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

Age

1 Male and female participants aged ≥ 1 to < 7 years of age at the time their legally authorised representative (parent or guardian) signs the informed consent.

Type of Participant and Disease Characteristics

2 All participants must have a diagnosis of NF1 with symptomatic inoperable PN where:

(a) Participants must have PN and at least one other diagnostic criterion for NF1 (Legius 2021)

- Six or more café-au-lait macules (> 5 mm in greatest diameter in prepubertal participants and > 15 mm in greatest diameter in post pubertal participants)
- Freckling in the axillary or inguinal region
- Optic pathway glioma
- Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities defined as bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging
- A distinctive osseous lesion such as: Sphenoid wing dysplasia, anterolateral bowing of the tibia or pseudoarthrosis of a long bone (Note: Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital plexiform neurofibroma)
- A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
- A parent with NF1 who meets the diagnostic criteria above

(b) A PN is defined as a neurofibroma that has grown along the length of a nerve and may involve multiple fascicles and branches. A spinal PN involves two or more levels with

connection between the levels or extending laterally along the nerve. A histologic confirmation of the PN is not necessary in the presence of consistent clinical and radiographic findings, but should be considered if malignant transformation of a PN is clinically suspected.

(c) Inoperable is defined as a 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; or unacceptable risk from the general anaesthetic as assessed by the Investigator

(d) Symptomatic is defined as clinically significant symptoms or complications caused by the PN, as judged by the investigator; symptoms may include, but are not limited to, pain, motor dysfunction and disfigurement (examples of complications include PN displacing trachea, or PN causing bladder obstruction and hydronephrosis).

3 Participants must have at least one measurable PN, defined as a PN 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. Participants 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 is symptomatic, inoperable and measurable by volumetric MRI analysis.

4 Performance status: Participants must have a Lansky performance of ≥ 70 except in participants who are wheelchair bound or have limited mobility secondary to a need for mechanical breathing support (such as an airway PN requiring tracheostomy or continuous positive airway pressure) who must have a Lansky performance of ≥ 40 (Appendix H).

5 Participants must have a BSA ≥ 0.4 and ≤ 1.09 m^2 at study entry (date of ICF signature).

Informed Consent

6 Mandatory provision of consent for the study signed and dated by a participant's legally authorised representative (parent or guardian) along with the paediatric assent form, when applicable as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this CSP.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1 Participants with confirmed or suspected malignant glioma or MPNST. Participants with low grade glioma (including optic glioma) not requiring systemic therapy are permitted.

2 History of malignancy except for malignancy treatment with curative intent with no known active disease ≥ 2 years before the first dose of study intervention and of low potential risk of recurrence.

3 Refractory nausea and vomiting, chronic gastrointestinal disease, inability to swallow the formulated product, or previous significant bowel resection that would preclude adequate absorption, distribution, metabolism, or excretion of selumetinib.

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

5 Participants with clinically significant cardiovascular disease as defined by the following:

- Known inherited coronary disease
- History of angina or acute coronary syndrome
- Symptomatic heart failure - New York Heart Association Class II to IV
- Prior or current cardiomyopathy
- Severe valvular heart disease
- Current or history of atrial fibrillation
- Baseline LVEF below LLN or < 55% measured by ECHO
- A QTcF > 450 ms
- Blood pressure > 95% percentile for age, height and gender measured as described in Appendix F.

6 As judged by the Investigator, any evidence of disease (such as severe or uncontrolled systemic disease, known moderate or severe hepatic impairment, active infection, active bleeding diatheses, or renal transplant), including any participant known to have hepatitis B, hepatitis C, or HIV which, in the Investigator's opinion, makes it undesirable for the participant to take part in the study.

7 Liver function tests:

- Total bilirubin > 1.5 × the ULN for age with the exception of those with Gilbert syndrome (≥ 3 × ULN)
- AST/ALT > 2 × ULN.

8 Renal Function:

- Creatinine clearance or radioisotope glomerular filtration rate < 60 mL/min/1.73 m^2.
- Serum creatinine > 0.8 mg/dL (for participants aged ≥ 1 to < 4 years) or > 1.0 mg/dL (for participants aged ≥ 4 years).

9 Participants with the following ophthalmological findings/conditions:

- Current or past history of RPED/CSR or RVO;
- Intraocular pressure > 21 mmHg (or ULN adjusted by age) or uncontrolled glaucoma (irrespective of IOP). Participants with known glaucoma that is clinically pain-free, has no clinically meaningful vision (light perception only or no light perception) and has increased IOP may be permitted.
- Participants with any other significant abnormality on ophthalmic examination should be reviewed for potential eligibility.

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

10 Have any unresolved chronic toxicity with CTCAE Grade ≥ 2 which are associated with previous therapy for NF1-PN (except hair changes such as alopecia or hair lightening)

11 Participants who have previously been treated with a MEKi (including selumetinib) and have had disease progression, or due to toxicity have either discontinued treatment and/or required a dose reduction.

12 Have had major surgery within 4 weeks of the first dose of study intervention, with the exception of surgical placement for vascular access. Have planned major surgery during the treatment period.

13 Have inadequate haematological function defined as:

- An absolute neutrophil count < 1500/μL
- Haemoglobin < 9g/dL
- Platelets < 100,000/μL
- Have had a transfusion (of red cells or other blood derived products) within the 28 days prior to study entry (date of ICF signature).

Prior/Concomitant Therapy

14 Have received or are receiving an IMP or other systemic NF1-PN target treatment (including MEKi) within 4 weeks prior to the first dose of study intervention, or within a period during which the IMP or systemic PN target treatment has not been cleared from the body (eg, a period of 5 'half-lives'), whichever is longer.

15 Has received radiotherapy in the 6 weeks prior to start of study intervention or any prior radiotherapy directed at the target or non-target PN.

16 Has received growth factors in the 7 days prior to study entry (date of ICF signature).

17 Receiving herbal supplements or medications known to be strong or moderate inhibitors of the CYP3A4 and CYP2C19 enzymes or inducers of the CYP3A4 enzyme unless such products can be safely discontinued at least 14 days or 5 half-lives (whichever is longer) before the first dose of study medication.

Prior/Concurrent Clinical Study Experience

18 Participation in another clinical study with an investigational product administered in the 30 days prior to the first dose of study intervention.

19 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.

Diagnostic Assessments

20 Inability to undergo MRI and/or contraindication for MRI examinations. Prosthesis or orthopaedic or dental braces that would interfere with volumetric analysis of target PN on MRI.

Other Exclusions

21 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

22 Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements

23 Previous treatment in the present study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

See Section 6.1.1 for details of food and drink restrictions prior to dosing or prior to PK sampling.

Participants should refrain from consumption of Seville oranges, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until after the final dose.

5.3.2 Activity

Participants/parents/guardians should be made aware of the need for good oral care during studies with selumetinib (Appendix E 7).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently dosed with the study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Participants may be rescreened once if the screening failure was due to a temporary condition. Any rescreening of participants must be done in consultation with the AstraZeneca Medical Monitor and any decision must be captured in the participant's medical notes.

Rescreened participants should be assigned the same participant number as for the initial screening. Participants should be rescreened once sufficient time has elapsed to feasibly allow correction of the reason for screen failure. All assessments must be repeated for rescreening unless they are within 28 days of starting the first study intervention.

However, rescreening should be documented so that its effect on study results, if any, can be assessed. These participants should have the reason for study withdrawal recorded in the eCRF as

"eligibility criteria not fulfilled" (i.e., participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (i.e., participants who are not dosed with the IP).

Participant enrolment is described in Section 6.3.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilised by a study participant according to the CSP.

6.1 Study Intervention Administered

6.1.1 Investigational Product

Details of the study intervention, selumetinib, are provided in Table 6.

Table 6 Investigational Products

Intervention name	Selumetinib	Selumetinib
Type	Drug	Drug
Dose formulation	Granule	Capsule
Unit dose strength(s)	[redacted] mg and [redacted] mg granule formulation in sprinkle capsules	[redacted] mg and [redacted] mg capsules
Dosage level(s)	Depends on outcome of dose-finding phase. (See Section 6.1.2)	[redacted] mg/m^2 bid (12 hours apart)
Route of administration	Oral	Oral
Use	Experimental	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and labelling	Study intervention will be supplied as [redacted] mg (white/white) and [redacted] mg (white/blue) sprinkle capsules in [redacted] 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 GCP Ordinance.	Study intervention will be supplied as [redacted] mg (white) and [redacted] mg (blue) capsules in [redacted] 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 GCP Ordinance.
[Current/former name(s) or alias(es)]	AZD6244 KOSELUGO®	AZD6244 KOSELUGO®

bid, twice daily; GCP, Good Clinical Practice; IMP, investigational medicinal product; NIMP, non-investigational medicinal product.

The initial proposed dose schema for the selumetinib granule formulation is shown in Table 7. Body

surface area will be calculated on Cycle 1, Day 1 and at intervals as shown in the SoA or more frequently, as appropriate, and the dosing regimen adjusted as needed. For participants with BSA in the range of 0.40 to 0.69 m^2 the proposed dose is expected to achieve the equivalent exposure of CCI mg/m^2 bid in participants with BSA ≥ 0.70 m^2. The modelling accounts for possible differences in absorption and metabolism (CYP enzyme maturation processes) in children under 3 years old. For BSA 0.7 m^2 and above, dosing recommendations with the granule formulation are in line with dosing recommendations for the selumetinib commercial capsule formulation. The final granule formulation dosing schema for selumetinib will be established during the dose-finding phase of the study (See Section 6.1.2)

Table 7 Initial Proposed Granule Formulation Dose Schema for Selumetinib

BSA (m^2)	Granules Dose (bid approximately 12 hours apart)	Dose level (mg/m^2)
0.40 - 0.49	CCI mg	CCI
0.50 - 0.59	CCI mg	CCI
0.60 - 0.69	CCI mg	CCI
0.70 - 0.89	CCI mg	CCI
0.90 - 1.09	CCI mg	CCI
1.10 - 1.29 [a]	CCI mg	CCI

[a.] In the rare circumstance that a participant is unable to transition to capsule selumetinib when they attain a BSA between 1.10 and 1.29 m^2 participants can continue to receive the granule formulation at the dose shown in Table 8.

Note that only one dose of selumetinib will be taken on C1D1; bid dosing will start on C1D2.
bid, twice daily; BSA, body surface area; C, cycle; D, day.

At enrolment participants must have a BSA within the range 0.40 to 1.09 m^2. Once participants attain a BSA between 1.10 and 1.29 m^2 they will be encouraged to completely transition to the capsule formulation, if feasible, although all participants must remain on the granule formulation until after they have completed their third cycle of treatment. Upon transition to the capsule formulation, PK sampling should be performed on Day 7 (range Day 4 to 14) as long as the participant has received 3 consecutive days of twice daily dosing with capsule formulation immediately prior to the PK day, see Section 8.6.1.1 for more details. The dosing schedule for the capsule formulation is shown in Table 8.

Table 8 Capsule Dose Schema for Selumetinib 25 mg/m^2 bid

BSA (m^2)	Capsule Dose (bid approximately 12 hours apart)	Dose level (mg/m^2)
1.10 - 1.29 m^2	30 mg	23.3 - 27.3
1.30-1.49 m^2	35 mg	23.5 - 26.9
1.50-1.69 m^2	40 mg	23.7 - 26.7
1.70-1.89 m^2	45 mg	23.8 - 26.5
≥ 1.90 m^2	50 mg	20.0 - 26.5

bid, twice daily; BSA, body surface area.

Granules from the sprinkle capsule should be mixed with a dosing vehicle prior to administration. Detailed instructions will be provided in the IMP handling instruction document or an equivalent document.

The time and content of meals on intensive PK sampling days (Cycle 1 Day 1, Cycle 2 Day 1 and, should the participant transition to capsule formulation, capsule dosing Day 7) should be recorded in source data.

Selumetinib granules are administered twice a day, approximately 12 hours apart. For participants aged ≥ 1 to < 4 years selumetinib granules can be taken without regard to food.

For participants aged ≥ 4 to < 7 years, on intensive PK sampling days (Cycle 1, Day 1 and Cycle 2, Day 1), selumetinib granules must be taken on an empty stomach (no food or drink other than water for 2 hours before and one hour after dosing, with the exception of vehicle and water to cleanse the palate). On other study treatment days selumetinib may be taken without regard to food.

Where capsules are taken, 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 one hour after dosing).

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.

6.1.2 Dose-finding Phase

The study includes an initial dose-finding phase designed to determine the dose schema for the granule formulation of selumetinib. Participants in the dose-finding phase at the recommended granule formulation dose schema will be analysed as part of the cohort for efficacy and safety at the primary analysis, the analysis after 25 cycles and the final analysis.

The physiologically-based PK model will be updated, if required, based on emerging PK data and the initial proposed dose schema may be adjusted.

Only participants enrolled in the Global Cohorts will participate in the dose-finding phase of the study.

Dose-finding Process

Data from three evaluable participants in Cohort 1 (participants aged ≥ 4 to < 7 years of age) are needed for the dose-finding phase. After the completion of at least one cycle of dosing in the first 3 evaluable participants, the SRC will evaluate the PK, safety, and tolerability of the granule formulation. To ensure that there are 3 evaluable participants in each dose finding phase, a maximum of 4 participants will be dosed. Should participants be classed as non-evaluable for the dose finding phase, additional participants will be dosed to ensure there is a minimum of 3 evaluable participants (maximum 4 evaluable participants). Dosing of additional participants in the study will be paused whilst the SRC convenes to assess the PK and safety data at the end of the dose-finding phase in the first 3 evaluable participants.

If the SRC determines that the selumetinib AUC0-12 and safety are within the acceptable criteria (See Section 6.1.2.1) dosing of additional participants into Cohort 1 will continue, and dosing in the dose finding phase for Cohort 2 (participants aged ≥ 1 to < 4 years) will commence (as described below).

If the SRC determines that the selumetinib AUC0-12 and safety are not within the acceptable criteria (See Section 6.1.2.1) dose adjustments will be made. Additional participants will be dosed into Cohort 1 in order to have an additional 3 evaluable participants. The dose-finding phase will continue to be assessed in this way until the granule formulation dose schema is identified and recommended for Cohort 1 (see Figure 2).

Once the selumetinib granule formulation dose schema is identified for Cohort 1, dosing in cohort 2 will commence in order to have 3 evaluable participants in Cohort 2 in the dose-finding phase. After the completion of at least one cycle of dosing in the first 3 evaluable participants, the SRC will evaluate the PK, safety, and tolerability of the granule formulation at this dose schema. To ensure that there are 3 evaluable participants in each dose finding phase, a maximum of 4 participants will be dosed. Should participants be classed as non-evaluable for the dose finding phase, additional participants will be dosed to ensure there is a minimum of 3 evaluable participants (maximum 4 evaluable participants). Dosing of additional participants in Cohort 2 will be paused whilst the SRC convenes to assess the PK and safety data in the first 3 evaluable participants.

If the SRC determines the granule formulation dose schema is within the acceptable criteria (See Section 6.1.2.1) dosing of additional participants in Cohort 2 will continue.

If the SRC determines the granule formulation dose schema is not within the acceptable criteria (See Section 6.1.2.1) and the dosing regimen will be amended, recruitment into Cohort 2 will continue in order to have an additional 3 evaluable participants in the dose-finding phase using the new dosing schema.

The dose finding phase will continue to be assessed in this way until the granule formulation dose

schema is identified and recommended for Cohort 2.

Following identification and recommendation of the granule formulation dose schema based on data from at least 3 evaluable participants, an additional SRC will be held for each of the cohorts following at least one cycle of dosing in approximately 6 evaluable participants. The SRC will evaluate the PK, safety and tolerability of the granule formulation at this dose schema.

If the SRC determines the granule formulation dose schema is within the acceptable criteria (See Section 6.1.2.1) dosing to the cohort will continue. If the SRC determines the granule formulation dose schema is not within the acceptable criteria (See Section 6.1.2.1). The dosing regimen will be amended, dosing to the cohort will continue in order to have 3 evaluable participants using the new dosing schema. The dose-finding phase for the cohort will re-start and an SRC will be held after 3 evaluable participants have completed at least one cycle of dosing and again after approximately 6 participants have completed at least one cycle of dosing.

An SRC will also be held for each of the cohorts following approximately one cycle of dosing in approximately 10 evaluable participants, the minimum sample size required for the cohort at the recommended granule dose schema (See Section 9.2). The SRC will evaluate the PK, safety, and tolerability of the granule formulation at this dose schema. Sample size may be re-evaluated in each cohort based on the observed PK variability in approximately CCI evaluable participants and therefore could increase for the final statistical analysis of PK data (scenarios are outlined in Table 17). The final analysis will compare the exposure to selumetinib for this study with that for the capsule formulation (SPRINT 25 mg/m^2).

In the situation where the dose schema is changed following evaluation of the PK, safety and tolerability, the SRC may decide to amend the dose schema for participants who started treatment in the study on an alternative dose schema.

6.1.2.1 Pharmacokinetics and Safety/Tolerability Acceptability Criteria for the Dose-finding Phase

The primary comparison will be single dose individual and median AUC0-12 derived from participants in this study with the AUC0-12 CCI percentile observed in the SPRINT study at CCI mg/m^2. Single dose AUC0-12 is recommended as minimal accumulation was observed in adult and paediatric participants following chronic bid dosing and sample size estimations are based on variability in the granule formulation from single dose AUC. In addition, assessment with single dose AUC0-12 allows timely dose adjustments if required and it is more probable than with multiple doses to obtain the full 12 hour profile for the AUC0-12 estimation.

Acceptance Criteria for PK Parameters (n = 3)

- If CCI participants AUC data are outside of the SPRINT CCI percentile and the median is within the CCI percentile; then the dose schema will not be adjusted and the recruitment will continue at this dose schema.
- If CCI participants AUC are outside of the SPRINT CCI percentile then the dose schema may be adjusted proportionally, based on the geometric mean NCA AUC for

SPRINKLE to that observed in the SPRINT study. Dose schema may not be adjusted if the geometric mean AUC0-12 is within CCI % of that of SPRINT. If the dose schema is adjusted, then the AUC will be re-assessed at the adjusted dose schema to confirm with an additional 3 participants that exposure is within the CCI percentile of SPRINT exposure.

Acceptance Criteria for PK Parameters (n = 6)

- If CCI participants AUC data are outside of the SPRINT CCI percentile and the median is within the CCI percentile; then the dose schema will not be adjusted and the recruitment will continue at this dose schema.
- If CCI participants AUC are outside of the SPRINT CCI percentile then the dose schema may be adjusted proportionally, based on the geometric mean NCA AUC for SPRINKLE to that observed in the SPRINT study. Dose schema may not be adjusted if the geometric mean AUC0-12 is within CCI % of that of SPRINT. If the dose schema is adjusted, then the AUC will be re-assessed at the adjusted dose schema to confirm with an additional CCI participants that exposure is within the CCI percentile of SPRINT exposure.

Safety Acceptance Criterion:

- No unacceptable safety findings as determined by SRC.

6.1.2.2 Definition of an Evaluable Participant for the Dose-finding Phase

- For PK: has a PK profile on Day 1 without any important protocol deviations potentially impacting the PK results.
- For Safety: if in the first cycle they receive at least 75% of study drug or experience a safety event. Has completed minimum safety evaluation requirements or experiences a safety event.

6.2 Preparation/Handling/Storage/Accountability

AstraZeneca will supply selumetinib granule formulation CCI mg (white/white) and CCI mg (white/blue) sprinkle capsules in CCI count bottles and CCI mg (white) and CCI mg (blue) capsules in CCI count bottles to the Investigator sites.

Selumetinib should be kept in a secure place according to the labelled storage conditions.

The Investigator or designee must confirm appropriate conditions have been maintained during transit for all selumetinib received and any discrepancies are reported and resolved before use of selumetinib.

Only participants enrolled in the study may receive selumetinib and only authorised site staff may supply or administer selumetinib. All selumetinib 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 intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Selumetinib may be delivered to a participant's home by a designated courier, if required.

Unused selumetinib should be returned to the site and disposed of according to local practice.

6.3 Measures to Minimise Bias: Randomisation and Blinding

The study is open-label and single arm; there is no randomisation.

At screening (Days -28 to -1) the Investigator or suitably trained delegate will:

1 Obtain signed informed consent from the legally authorised representative (parent or guardian) of the participant and assent from the participant (if deemed appropriate as per local regulations) before any study specific procedures are performed. Informed consent may be signed within 42 days of dosing window if it is more convenient for the site and families. If laboratory procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the legally authorised representative (parent or guardian) of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of the first dose of study intervention.
2 Obtain a unique 7-digit enrolment number (E-code), through the IRT in the following format PPD This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
3 Determine participant eligibility (see Section 5.1 and Section 5.2 for inclusion and exclusion criteria, respectively).

On Day 1, once the participant is confirmed to be eligible, the Investigator, or suitably trained delegate, will:

1 Log in to IRT for treatment assignment or registration.
2 Participants may be enrolled but not treated. If the participant is not treated, the IRT should be accessed to terminate the participant in the system.
3 The IRT will be used to track drug supply.
4 Participants will begin treatment on Day 1. Participants must not be treated unless all eligibility criteria have been met.

If a participant withdraws from the study, then his/her enrolment code cannot be reused.

Investigators should keep a record (i.e., the participant screening log) of participants who entered screening.

Procedures for Handling Incorrectly Enrolled Participants

Participants who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study intervention. There can be no exceptions to this rule. Participants who are enrolled but subsequently found not to meet all the eligibility criteria must not be started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca Medical Monitor immediately, and a discussion should occur between the AstraZeneca Medical Monitor and the Investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca Medical Monitor must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

6.4 Study Intervention Compliance

When participants are dosed at the site (eg, PK days), they will receive study intervention directly from the investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

Parents/guardians of the participant will complete a daily drug diary to record the dates and times on which selumetinib is taken.

When participants (self/parent/guardian) administer study intervention at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by counting returned sprinkle capsules or capsules and reviewing the Drug Diary at each site visit and documenting in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of selumetinib sprinkle capsules or capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

The Investigational Product Storage Manager is responsible for managing the study intervention from receipt by the study site until the destruction or return of all unused study intervention.

6.5 Concomitant Therapy

Any medication, procedure or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving from the time of screening or receives during the study including the 30 day safety follow-up phase following the last dose of study intervention must be recorded in the eCRF along with:

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

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Unless considered to be clinically indicated, participants should avoid taking other additional non-study medications that may interfere with the 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 s**hould be avoided until after the PK assessment on Cycle 2, Day 1. During the remainder of the study (i.e., from Cycle 2, Day 2 onwards), if concomitant use of selumetinib with strong or moderate CYP3A4 and CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Appendix I. The participant should be monitored closely for potential toxicities. The AstraZeneca Medical Monitor should be contacted to discuss whether these participants should be withdrawn or, if deemed to be deriving a clinical benefit, can continue in the study.

In vitro selumetinib is an inhibitor of OAT3. The potential for a clinically relevant effect on the PK of concomitantly administered substrates of OAT3 cannot be excluded and they should be given with caution.

Additional Prohibited Concomitant Medication when taking Capsules

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 participant may receive from selumetinib is approximately 261.6 mg/day. Therefore, participants should discontinue any supplemental vitamin E at least 7 days prior to transitioning to selumetinib capsules, and should not take any supplemental vitamin E while receiving selumetinib capsules. High doses of vitamin E have been reported to cause bleeding and interfere with blood coagulation processes. Note that this restriction does not apply to participants being treated with the selumetinib granule formulation as it does not contain D-α-tocopheryl polyethylene glycol 1000 succinate.

Selumetinib should be administered with caution in participants who are also receiving concomitant coumarin anticoagulant medications (eg, warfarin). These participants should have their INR monitored/anticoagulant assessments conducted more frequently and the dose of the anticoagulant should be adjusted accordingly.

Prohibited medications are shown in Table 9.

Table 9 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 longer) prior to the first dose of study intervention. Not allowed during the study.
MEK inhibitor	Not allowed for 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Not allowed during the study (with the exception of selumetinib study intervention).
Other systemic NF1-PN target treatment	Not allowed for 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Not allowed during the study.
Radiotherapy	Not allowed for 6 weeks prior to the start of intervention. Radiotherapy (before or during the study) not allowed on target or non-target PNs.
Growth factors	Not allowed within the 7 days prior to study entry (date of ICF signature).
Blood (red cells or other blood derived products) transfusion	Not allowed within the 28 days prior to study entry (date of ICF signature).
Multivitamins containing vitamin E	Must be stopped 7 days prior to initiation of selumetinib capsules. Not allowed during the study while being treated with selumetinib capsules. Permitted while being treated with selumetinib sprinkle capsules.
Herbal supplements or medications known to be strong or moderate inducers of CYP3A4, or strong or moderate inhibitors of CYP3A4 and CYP2C19 (Appendix I)	Must be safely discontinued at least 14 days or 5 half-lives (whichever is longer) 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 2, Day 1. During the remainder of the study (i.e., from Cycle 2, Day 2 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 I.

CYP, cytochrome P450; ICF, informed consent form; IMP, investigational medicinal product; MEK, mitogen activated protein kinase; NF1, neurofibromatosis type 1; PK, pharmacokinetics; PN, plexiform neurofibroma.

6.6 Dose Modification

Specific guidance for the management of AEs, including interruption or reduction of treatment with selumetinib, may be considered for particular events of special interest (eg, diarrhoea, dyspnoea, rash, asymptomatic reduction in LVEF, and visual disturbance), as indicated in the algorithms provided in Appendix E.

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 intervention may be restarted at the discretion of the Investigator. If restarted, it must be at a reduced dose as shown in Table 10 and Table 11. If the AE does not resolve to CTCAE Grade 1 or less within 4 weeks of onset, study intervention must be permanently terminated unless otherwise specified in the Guidance for Management of Specific AEs (Appendix E).

The dose modification procedure is shown in Table 10 and Table 11. Two step dose modification is applied in the study. Any participants with 2 prior dose reductions who experience a toxicity that would cause a third dose reduction must be discontinued from study intervention.

Dose must not be re-escalated following dose reduction apart from to account for increase due to BSA, in accordance with Table 10 and Table 11. For example, if a participant has a BSA of 1.2 m^2 and starts on a capsule dose of 30 mg bid and then has a dose reduction to 25 mg AM, 20 mg PM then a subsequent BSA increase to 1.4 m^2 would mean the participant should be dose adjusted to 25 mg bid.

Note that if selumetinib treatment is interrupted for > 4 weeks for any reason other than AEs related to selumetinib eg, investigations, unplanned procedures and AEs unrelated to selumetinib, re-start of treatment must be discussed with the Medical Monitor.

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 participant, 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 Medical Monitor.

As the initial proposed dose schema for the selumetinib granule formulation may be adjusted based on emerging safety, tolerability, and PK data, the dose reductions shown in Table 10 may not

include all scenarios. The principles for the granule formulation dose reduction are as follows:

- The reduced dose should be 25% lower than the non-tolerated dose.
- The reduced dose should be rounded down to the nearest achievable dose using the same granule formulation strengths, to minimise dosing errors.

Table 10 Granule Formulation Dose Modification Procedure based on Initial Proposed Granule Dose Schema

Body surface area (m^2)	Selumetinib dose (mg) bid [a] starting dose	First selumetinib dose (mg) bid reduction	Second selumetinib dose (mg) bid reduction
0.40 – 0.49	CCI		
0.50 – 0.59			
0.60 – 0.69			
0.70 – 0.89			
0.90 – 1.09			
1.10 – 1.29 [b]			

a. Actual dose in mg administered every 12 hours to achieve exposure approximately equivalent to capsule in SPRINT; target median AUC = CCI ng/mL at selumetinib dose CCI mg/m^2 BSA.
b. In the rare circumstance that a participant is unable to transition to capsule selumetinib when they attain a BSA between 1.10 and 1.29 m^2 participants can continue to receive the granule formulation at the dose shown in Table 8, and dose modifications should be as per Table 11.

AUC, area under the concentration-time curve; bid, twice daily; BSA, body surface area.

Table 11 Capsule Dose Modification Procedure

Body surface area (m^2)	Selumetinib starting dose (mg) [a]		First selumetinib dose (mg) reduction		Second selumetinib dose (mg) reduction	
	AM	PM	AM	PM	AM	PM
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 bid.

bid, twice daily.

6.7 Continued Access to Study Intervention after the End of the Study

As described in Section 4.4, the study will remain open until all participants have discontinued study intervention and completed their last expected visit/contact.

After the participant's last visit, AstraZeneca will continue to supply selumetinib to participants whilst they are still receiving clinical benefit or until meeting any other discontinuation criteria as defined in Section 7.1.

AstraZeneca will continue to supply selumetinib in the continued access phase of this study while, in the opinion of the Investigator, the participant is benefiting.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the Investigator. AstraZeneca will work with the Investigator to transition the participant(s) to alternative supply, where possible.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participant(s) currently receiving treatment with selumetinib may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

In the following section the term "participant" also refers to the participant's legally authorised representative acting on their behalf.

7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue selumetinib. See the SoA (Table 2 and Table 3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

The Investigator should instruct the participant to contact the site before or at the time if study intervention is stopped. A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT. All study intervention should be returned by the participant at their next on-site study visit or unscheduled visit.

Participants may be discontinued from study intervention in the following situations:

- Disease progression based on the Investigator's decision.
- Investigator determination that the participant is no longer benefiting from study intervention.
- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6).
- Participant decision. The participant is at any time free to discontinue treatment, without prejudice to further treatment. A participant who discontinues treatment may continue to

participate in the study (eg, for safety) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.2).

- Severe non-compliance with the CSP as judged by the Investigator or AstraZeneca.
- Pregnancy.
- Initiation of systemic therapy for NF1-PN, including another investigational agent.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

7.2 Participant Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance, or administrative reasons. This is expected to be uncommon.
- A participant who considers withdrawing from the study must be informed by the Investigator about modified follow-up options to ensure the collection of endpoints and safety information including new AEs and follow-up on any ongoing AEs and concomitant medications (eg, telephone contact at 30 days (+ 7 days) after study intervention is discontinued, a contact with a relative or treating physician, or information from medical records).
- At the time of withdrawal from the study, if possible, an End of Treatment visit should be conducted as shown in the SoA (Table 2). See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.
  - The participant will discontinue selumetinib and be withdrawn from the study at that time.
- If the participant 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 participant withdraws from the study, it should be confirmed if he/she still agrees for existing samples to be used in line with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

Participants who decline to continue participation in the study, including telephone contact, should be documented as “withdrawal of consent” rather than “lost to follow-up.” Investigators should document attempts to re-establish contact with missing participants throughout the study period. If contact with a missing participant is re-established, the participant should not be considered lost to follow-up and evaluations should resume according to the CSP.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel them on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to be lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) obtained before signing of the ICF may be utilised for screening or baseline purposes with consent of the legally authorised representative (parent or guardian) of the participant provided the procedures met the CSP-specified criteria and were performed within the time frame defined in the SoA.

8.1 Administrative and General/Baseline Procedures

N/A

8.2 Efficacy Assessments

8.2.1 Imaging of the Target PN

In 2013, consensus recommendations for the imaging of PN were issued by an international working group (REiNS) who recommended MRI volumetric PN assessment as preferable to all other MRI analysis techniques. Magnetic resonance imaging with volumetric analysis is

recommended to sensitively and reproducibly evaluate changes in PN 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 PN size (Dombi et al 2013).

Extent of PN in patients with NF1 can be very substantial, and may not allow for all PNs to be followed using volumetric MRI. Both target and non-target PNs must be symptomatic, measurable and inoperable. Prior to starting treatment on this study, the investigator must select the target PN. The target PN is defined as the clinically most relevant PN (signs/symptoms/complications which have the most impact on the patient in the opinion of the Investigator), which is measurable by volumetric MRI analysis. If there is a second PN that is also considered clinically relevant, the investigator may select this as a non-target PN; only one non-target PN can be selected. AstraZeneca's appointed imaging CRO will measure the target PN and non-target PN (if applicable). The management of participants will be based upon the results of the PN assessments conducted by the Investigator using their standard of care methods.

The MRI images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging CRO for quality control, storage, and for ICR. The details about target PN location (most clinically relevant PN) and non-target PN location (if relevant) will also be collected to provide to the independent reviewer. Digital copies of all original scans should be stored at the Investigator site as source documents. An ICR of images will be performed for the assessment of efficacy according to the REiNS criteria as stated in the exploratory endpoints. Results of these independent reviews will not be communicated to Investigators, and results of Investigator PN assessments will not be shared with the central reviewers.

Screening imaging evaluation:

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

On study imaging evaluation:

Unless clinically indicated otherwise, and as defined in Table 2, volumetric MRI of the target and non-target PNs should be performed at every 4 cycles (16 ± 1 weeks) relative to the date of first dose for the first 13 cycles, and subsequently every 6 cycles (24 ± 1 weeks). The MRI data for participants who discontinue selumetinib prior to Cycle 25 will be collected if a suitable MRI is performed as standard of care until the time when they would have completed 25 cycles of treatment, or they commence an alternative systemic NF1-PN treatment, whichever is the earliest.

The REiNS assessment criteria of volumetric MRI of the target PN performed by the central imaging vendor are as follows:

- Complete response: disappearance of the target PN. The CR is considered unconfirmed at first detection and confirmed when observed again at a consecutive scan within 3 to 6 months.
- Partial Response: decrease in the volume of the target PN by 20% or more compared to baseline. The partial response 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 partial response or PD.
- Progressive Disease: 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) which is unequivocally and completely distinct and separate from the target PN and the non-target PN, or unequivocal progression of an existing non-target 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.

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

8.2.2 Objective Response Rate

Objective response rate is defined as the percentage of participants with measurable disease who have a confirmed CR (defined as disappearance of the target PN, confirmed by a consecutive scan within 3 to 6 months after the first 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 the first response) as determined by ICR per REiNS criteria.

8.2.3 CCI

CCI is defined as the time from CCI until the CCI CCI (by ICR per REiNS criteria) of CCI CCI Progressive disease is an increase in target PN volume by 20% or more compared to baseline or compared to the time of best response after documenting a PR. The appearance of new PN (with the exception of new discrete subcutaneous neurofibromas) or unequivocal progression of existing clinically relevant non-target PN is also considered PD.

8.2.4 CCI

CCI is defined as the time from the date of CCI CCI until date of CCI CCI as determined by ICR per REiNS criteria).

8.2.5 CCI

CCI is defined as the time from CCI until the CCI

CCI

8.2.6 CCI

CCI is defined as the time from CCI until the CCI CCI The first CCI should coincide with that used for the CCI

8.2.7 Clinical Outcome Assessments

A COA is any assessment that may be influenced by human choices, judgment, or motivation and may support either direct or indirect evidence of treatment benefit. A COA can be reported by a participant (patient-reported outcomes), a clinician, an observer, or through a performance-based assessment (FDA-NIH BEST Resource). A COA may be used in clinical studies to provide either direct or indirect evidence of treatment benefit. It is important to examine the impact of therapy on symptoms, function, and other CCI of the participant to aid understanding of the risk-benefit profile. The following COA instruments will be administered in this study:

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

CCI

Where possible each COA assessment should be completed by the CCI CCI

8.2.7.1 CCI CCI

The CCI is an CCI measurement used to assess CCI CCI , or for older individuals that are CCI It incorporates CCI Each behaviour is scored between CCI CCI for this study the CCI for several minutes and then determines the score for each category. It has been validated in CCI CCI The same group later updated the CCI CCI however, it has not been validated in an NF1 patient population specifically. This will be completed daily in the evening for 7 days after the visits specified in the SoA. The CCI will be completed by the CCI CCI at time of study entry (date of signature of consent) or those who in the opinion of the Investigator are CCI .

A copy of the scale is provided in Appendix J 1.

CCI

The CCI is a CCI measure of CCI CCI are presented to the child, who will then CCI giving a score. The scale shows a close linear relationship with CCI across the age range of CCI CCI In this study, the CCI will be used to assess CCI in children aged CCI years of age at time of study entry (date of signature of consent) CCI CCI daily in the evening according to the schedule specified in the SoA (Table 2).

A copy of the scale is provided in Appendix J 2.

8.2.7.2 CCI

The CCI is a CCI measure used to assess CCI CCI This will provide complementary information to the CCI CCI to inform change over time in CCI while minimising recall bias.

A copy of the scale is provided in Appendix J 3.

8.2.7.3 CCI

The CCI is a CCI measure used to CCI CCI. It uses as a CCI and will be used as a supportive assessment to the CCI and CCI to ensure a common assessment across age range.

A copy of the scale is provided in Appendix J 4.

8.2.7.4 CCI

The CCI is a widely accepted measure for CCI CCI

The CCI are multidimensional CCI CCI. The CCI is a brief standardised CCI scale with good reliability and validity, which includes both CCI It consists of a CCI

The CCI have been developed in CCI. In this study, CCI will be used. CCI CCI will be used in this study. The questionnaire takes approximately CCI minutes to complete and will be used for participants aged CCI years as shown in Table 12.

The CCI consists of CCI . It is a CCI and the CCI version will be used in this study for participants CCI years as shown in Table 12.

Table 12 CCI

CCI

A copy of the scale is provided in Appendix J 5.

8.2.7.5 CCI

A CCI will be used to ensure that CCI Information on CCI will be collected, including CCI The survey will be completed by CCI on paper in the evening for 7 days prior to the visits specified in the SoA and verified by the Investigator or delegate.

8.2.7.6 Palatability

An assessment of palatability (the overall appreciation of the product in relation to its smell, taste, aftertaste and texture) will be conducted using a parent-reported observer palatability assessment. It is a 3-item measure with dichotomous responses, assessing willingness to swallow and other observed behaviour on administration of an oral medication.

A copy of the palatability scale is provided in Appendix J 6.

8.2.7.7 Administration of Electronic Questionnaires

Questionnaires will be completed by the participant's parent or guardian (or, where relevant, the participant) using electronic devices at the time points indicated in the SoA. The questionnaires may be completed at study sites if the assessment time point coincides with a scheduled site visit; otherwise, the questionnaires should be completed at home.

Each site must allocate the responsibility for the administration of the instruments to a specific individual (eg, a research nurse or study co-ordinator) and, if possible, assign a backup person to cover if that individual is absent.

Approximately 10 to 20 minutes is required for participants to complete the questionnaires.

The below instructions should be followed when collecting questionnaire data via an electronic device:

- At the site, the questionnaires should be completed prior to any other study procedures or discussions (following informed consent), including medication treatments, and before discussion of disease progression that could bias the responses to the questions.
- The questionnaires should be completed in a quiet and private location.
- The parent/guardian or participant should be given sufficient time to complete the questionnaires at his/her own speed.
- The research nurse or appointed site staff should explain to the parent/guardian or participant the value and relevance of these data so they are motivated to comply with questionnaire completion.
- The research nurse or appointed site staff should stress that the information is not routinely shared with study staff. Therefore, if the participant has any medical problems, the parent/guardian or participant should discuss them with the doctor or research nurse separately from the assessment.
- The research nurse or appointed site staff must train the parent/guardian or participant on how to use the electronic device using the materials and training provided by the ePRO vendor.
- The research nurse or appointed site staff must provide guidance on whom to call if there are problems with the device when the parent/guardian or participant is completing the questionnaires at home.
- All questionnaires must be completed using the electronic device; paper questionnaires are not allowed in this study.
- The research nurse or appointed site staff must remind participants that there are no right or wrong answers and avoid introducing bias by not clarifying items.

Completion of Questionnaires at Clinic Visits:

- If a parent/guardian or participant uses visual aids (eg, spectacles or contact lenses) for reading and does not have them when he or she attends the clinic, the participant will be exempted from completing the questionnaires at that clinic visit.
- Site staff must not complete the ePRO questionnaires on behalf of the participant.
- Site staff must provide questionnaires available in the language that the participant speaks and understands. Questions must not be read in an available language and translated into another language for the participant.
- It is critical that the questionnaires are completed as specified in the SoA to capture the effect of study intervention.

Completion of Questionnaires at Home:

- Reminders should be sent to parent/guardian or participants at home as needed to ensure compliance with the assessment schedules.
- The same parent/caregiver should complete the questionnaires at home or at the site.

- Finally, the research nurse or appointed site staff will review the completion status of questionnaires during site visits, and document the reason(s) why a parent/guardian or participant could not complete assessments, in the source documents and in the designated eCRF. If compliance drops to or below 85%, they will be flagged in the routine compliance report generated by the ePRO system, and appropriate action will be taken (eg, discussion with parent/guardian or participant to improve compliance, a check in call from the site to ask the parent/guardian or participant if they have any difficulties in completing questionnaires on schedule, etc).

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 2 and Table 3).

8.3.1 Physical Examination Including CCI

A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, hematologic/lymphatic and CCI CCI Targeted physical examinations are to be used by the Investigator on the basis of clinical observations and symptomatology.

An abbreviated physical examination will include, at a minimum, assessments of the general appearance, respiratory and cardiovascular systems, skin and abdomen (liver and spleen) as clinically indicated.

Physical examination will be performed at time points as specified in the SoA; Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as AEs, see Section 8.4.5 for details.

If unexplained muscle weakness or myalgia (muscle pain) occurs, the participant 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.

8.3.2 Height and Weight

Height and weight will be measured at the times outlined in the SoA. The participant's height will be recorded in cm and weight will be recorded in kg. Height and weight measurements will be performed in light clothing and with shoes off. Children under 2 years of age and those who are unable to stand stably enough to be measured in the standing position should be measured in the supine position on a measuring board (eg, Kiddimeter).

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

Height: The participants 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 participants with known leg length discrepancy due to limb hypertrophy, height should be measured with the participant bearing weight on the limb without hypertrophy.

Body Surface Area should be calculated using the formula derived by Mosteller:

- √ (weight (kg) x height (cm) / 3600

8.3.3 Vital Signs

Vital signs will be performed at timelines as specified in the SoA.

Temperature, pulse rate, oxygen saturation by pulse oximetry, respiratory rate, and BP will be assessed.

Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).

Three consecutive BP readings will be recorded at intervals of at least one minute. The average of the 3 BP readings will be recorded on the eCRF.

8.3.4 Electrocardiograms

An ECG will be performed at time points as specified in the SoA.

Single 12-lead ECGs will be obtained locally at the site. Electrocardiograms will be evaluated at the times outlined in Table 2 and Table 3 using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Participants that were enrolled on CSP Version 1.0 (therefore with QTcB as an exclusion criterion at screening), should have both QTcB and QTcF collected at all timepoints throughout the study, and QTcF should be retrospectively calculated and reported for all visits that have previously occurred. Participants should be supine (where possible) and at rest 5 minutes prior to recording the ECG.

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 8.3.5) and on occurrence of any cardiorespiratory AEs with no obvious diagnosis. For participants 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.

8.3.5 Echocardiogram

An ECHO to assess LVEF will be performed at the visits as shown in the SoA. Participants should be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (i.e., accurate to 1% and not estimated to 5%).

Left ventricular ejection fraction, end diastolic, and end systolic left ventricular volumes should be recorded at each ECHO assessment.

Participants experiencing an asymptomatic LVEF reduction or left ventricular systolic dysfunction should be managed according to the algorithm provided in Appendix E 1.

Participants 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 follow-up ECHO, ECG, vital signs and weight performed after 30 days to evaluate the potential for reversibility.

An ECHO will also be carried out if a participant develops signs and/or symptoms suggestive of deterioration in left ventricular function/cardiac event.

A further ECHO 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.

If a participant has had an ECHO performed within 4 weeks prior to treatment discontinuation, the discontinuation visit ECHO scan is not required unless clinically indicated.

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

8.3.6 Ophthalmologic Examinations

An ophthalmologic examination (age appropriate best corrected visual acuity, IOP and slit-lamp or indirect fundoscopy) will be evaluated at the times outlined in the SoA, and as clinically indicated whilst the participant is on study intervention. The participant should be examined using the same machine and operator throughout the study wherever possible.

If a participant experiences symptoms of visual disturbance (including blurring of vision), a complete ophthalmological examination, including a slit-lamp or indirect fundoscopy examination, must be performed. If an abnormality is detected, fundus photography and an optical coherence tomography scan can also be performed where required. Adverse events are to be managed according to Appendix E 3.

If a retinal abnormality prior to or at the 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. Abnormalities should be followed up.

8.3.7 Knee/Wrist MRI/X-ray

Yearly growth assessments require integration of information including height measurements 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 MRI/X-ray of the knee will be performed at screening as specified in Table 2 and Table 3, and if clinically indicated, to monitor growth plates for any signs of physeal dysplasia. The imaging modality that is used at baseline (MRI/X-ray) must be used at all follow-up visits throughout the study. A wrist MRI/X-ray is acceptable if it is not possible to perform knee MRI/X-ray. The joint imaged (left/right, wrist/knee) must be consistent throughout the study, except occasions where MRI/X-ray of the joint imaged at baseline is not possible. Where feasible the knee/wrist MRI/X-ray will be performed at the same time as the PN volumetric MRI.

The investigator should regularly look for signs of physeal dysplasia (eg, joint pain and fatigue after exercising, abnormal gait, and spine irregularities). 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.

8.3.8 Performance Status

Performance status will be measured as indicated in the SoA; the Lansky performance scale is described in more detail in Appendix G.

Any significant change from baseline or screening must be reported as an AE.

8.3.9 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the visits indicated in the SoA.

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.

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

The laboratory variables shown in Table 13 will be measured.

Table 13 Laboratory Safety Variables

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

a. Creatinine clearance and glomerular filtration rate to be calculated at screening and if clinically indicated.
b. Urine microscopy will be assessed if other urinalysis measurements are abnormal or if clinically indicated
c. Urea or blood urea nitrogen based on local site practice.
d. Creatine Kinase to be assessed in accordance with the schedule of assessments and if unexplained muscle weakness or myalgia (muscle pain) occurs. See Section 8.3.1 for additional information.
e. 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 intervention) or for any cardiorespiratory events with no obvious diagnosis. If troponin assessments are not available, per local practice, CK-MB isoform should be assessed. Participants should be managed according to the algorithm provided in Appendix E 2.

B, blood; CK-MB, creatine kinase-myocardial band; LLN, lower limit of detection; LVEF, left ventricular ejection fraction; P, plasma; S, serum; U, urine.

In case a participant shows 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, for further instructions.

The Investigator should assess the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.4.5.

All participants with Grade 3 or 4 laboratory values at the time of completion or discontinuation from study intervention must be followed and have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.3.10 Other Safety Assessments

8.3.10.1 CCI

Appropriate CCI will be used based on age of the participant at the time of the assessment:

CCI

CCI

The CCI is one of the most reliable and widely used tests for CCI CCI . The CCI is derived from the CCI CCI . It can be administered in CCI minutes CCI The CCI of participants **aged** CCI **years** will be evaluated with this test.

CCI

The CCI consists of CCI CCI CCI The CCI consist of CCI In the context of this study CCI CCI Both CCI include CCI . The CCI CCI are used to compute the CCI score and CCI scores: CCI The CCI measure aspects of CCI The CCI CCI takes approximately CCI minutes to complete CCI The CCI of participants **aged** CCI **years** will be evaluated with this test.

CCI

The CCI, currently in its CCI edition, is a widely used and accepted test of CCI. In the context of this study, **only the** CCI **is required**, there is no need to perform CCI
The CCI is validated for administration to people aged CCI years (there is no upper limit) and takes CCI minutes to complete. The CCI of participants **aged** CCI **years** will be evaluated with this test CCI

8.4 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.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of signature of the ICF until 30 days after the last dose of selumetinib or 25 cycles of treatment, whichever is earlier. For participants taking part in the long term safety follow-up (participants < 5 years of age), after 25 cycles of treatment or end of treatment, adverse events causally related to selumetinib will be collected until they complete the study in accordance with Table 3. No AEs will be collected for participants who are > 5 years of age who remain in the study after 25 cycles of treatment.

SAEs will be collected from time of signing the ICF throughout a subject’s participation in the study.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant’s last AE assessment in the study are 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 participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse Event Variables

The following variables will be collected for each AE:

- The AE (verbatim)
- The date and time when the AE started and stopped
- The CTCAE grade/max CTCAE grade/changes in CTCAE grade
- Whether the AE is serious or not (Appendix B)
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to Investigational Product
- If the AE caused participant's withdrawal from study (yes or no)
- Administration of treatment for the AE
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Adverse event 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

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 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).

8.4.3 Causality Collection

The Investigator should assess causal relationship between Investigational Product 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 Investigational Product?'

For SAEs causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is

implied as 'yes'.

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

8.4.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: '**Has 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.

8.4.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests, vital signs, physical examinations, ECGs, ECHO scans and ophthalmological examinations will be summarised in the Clinical Study Report.

Deterioration as compared to baseline in CSP-mandated laboratory tests, vital signs, ECGs, echocardiogram scans and ophthalmological examinations should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the investigational product 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 intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign/ECG/ECHO is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign/ECG/ECHO will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated 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.

8.4.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ 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.

8.4.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the study intervention 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 symptoms, or the progression of existing symptoms, of NF1-PN should be considered as disease progression and not an AE. Events which are unequivocally due to disease progression should not be reported as an AE during the study.

8.4.8 Disease under Study

Symptoms of disease under study are those which might be expected to occur as a direct result of NF1-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 study intervention.

8.4.9 Reporting of Serious Adverse Events

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

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

The designated AstraZeneca representative will work with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within one 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 will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one 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 EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone followed by completion of a paper SAE form.

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

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

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

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as de-scribed in the European Clinical Trials Regulation (EU) No 536/2014. All Suspected Unexpected Serious Adverse Reactions (SUSARs) to investigational medicinal product will be reported to the EudraVigilance database within the required regulatory timelines.

8.4.10 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study participant has received any study intervention.

8.4.10.1 Maternal Exposure

Not applicable due to age of participants.

8.4.10.2 Paternal Exposure

Not applicable due to age of participants.

8.4.11 Medication Error, Drug Abuse, and Drug Misuse

8.4.11.1 Timelines

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, i.e., immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within **one** (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, drug abuse, or drug misuse (see Section 8.4.9) and **within 30 days** for all other events.

8.4.11.2 Medication Error

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

The full definition and examples of medication error can be found in Appendix B 4.

8.4.11.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP/study intervention or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.11.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study intervention(s) or AstraZeneca NIMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4.12 Medical Device Deficiencies

This section is not applicable for this study.

8.4.13 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the 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 8.4.9. Adverse events of special interest based on examinations and tests should be reported in accordance with Section 8.4.5.

Adverse events of special interest are shown in Table 14.

Table 14 Adverse Events of Special Interest

AESI	MedDRA Preferred Terms 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.
Physeal dysplasia	Metaphyseal dysplasia; Multiple epiphyseal dysplasia; Arthralgia; Joint stiffness; Joint hyperextension; Gait disturbance; Short stature.
Choking on the capsule	Choking; Retching.

AESI, adverse event of special interest; MedDRA, Medical Dictionary for Regulatory Activities.

8.5 Overdose

For this study, any dose of selumetinib greater than the assigned dosage will be considered an overdose. There is currently no specific treatment in the event of overdose of selumetinib, and possible symptoms of overdose are not established.

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 on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel should inform appropriate AstraZeneca representatives 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 one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.9) and **within 30 days** for all other overdoses.

8.6 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix C.

Human blood samples will be disposed as soon as possible after the test outlined in this document is complete.

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

Remaining unused PK or PD samples may be used for exploratory biomarker analysis as indicated in Section 8.7 and is subject to agreement in the ICF and also according to local requirements.

8.6.1 Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of selumetinib and N-desmethyl selumetinib as specified in the SoA (Table 2).
- Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the sponsor, e.g., for safety reasons. The timing of sampling

may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

- Plasma samples will be used to analyse the PK of selumetinib and N-desmethyl metabolite. Samples collected for analyses of study intervention (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Pharmacokinetic samples will be analysed at bioanalytical test sites operated by or on behalf of AstraZeneca. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

8.6.1.1 Collection of Samples

Blood samples will be collected for measurement of selumetinib and N-desmethyl selumetinib as shown in Table 15.

Table 15 Pharmacokinetic Sampling Schedule

	Time [a]
Cycle 1, Day 1 [b]	Pre-dose and 1, 2, 3, 4, 6, 8, 10-12, and 18-24 hours post-dose
Cycle 2, Day 1 [c]	Pre-dose and 1, 2, 3, 4, 6, 8, and 10-12 hours post-dose
Cycle 5, Day 1	Pre-dose
Cycle 13, Day 1	Pre-dose
Cycle 25, Day 1	Pre-dose
Transition from granule to capsule formulation [d]	Pre-dose, 0.5, 1.5, 3, 6, and 10-12 hours post-dose

a. Pre-dose within 10 minutes prior to dosing. Time allowance for samples 1, 2, 3 and 4 hours post-dose: ± 15 minutes, 6 and 8 hours post-dose ± 30 minutes. On Cycle 2, Day 1, the second dose of selumetinib should be taken after the 12 hour sample.
b. Single dose (morning only) will be administered on Cycle 1, Day 1; bid continuous dosing will start from Cycle 1, Day 2.
c. For operational reasons, the pharmacokinetic sampling on Cycle 2, Day 1 can take place on any day between Cycle 1, Day 24 and Cycle 2, Day 8 as long as the participant has received 3 consecutive days of bid dosing immediately prior to the PK day. Every effort should be made to conduct PK sampling within the window. However, if for unforeseen reasons this is not possible, PK sampling can be performed at any time from 7 days prior to Cycle 2, Day 1 to end of Cycle 3 provided the participant has received 3 consecutive days of dosing immediately prior to the PK day.
d. Samples should be taken on Day 7 (range Day 4 to Day 14) as long as the participant has received 3 consecutive days of twice daily dosing with capsule formulation immediately prior to the PK day.

PK, pharmacokinetic.

8.6.1.2 Determination of Drug Concentration

Samples for determination of selumetinib and N-desmethyl selumetinib in plasma will be assayed by CCI bioanalytical laboratories 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, if performed, will be reported in a separate Bioanalytical Report.

8.6.2 Pharmacodynamics

Where possible, optional blood samples for exploratory analysis of pharmacodynamic biomarkers in PBMCs can be taken during Cycle 1, Day 1. This analysis includes, but may not be limited to, pERK inhibition. This would require additional blood volume on a PK profile day, in addition to the volume required for PK samples and for safety samples. In line with the European Condition requirement that blood volume should not exceed 1% of the total blood volume at any single time, the samples for pERK can only be collected only in patients ≥ 27 kg. For a patient that is 6 years old this would mean that they would have to be approaching the 98th percentile on the UK-WHO growth chart (UK WHO Growth Chart). It is therefore considered these samples would be collected only in the oldest and largest of children. Samples should be taken according to Table 16.

Table 16 Pharmacodynamic Sampling Schedule

Visit	Time [a]
Cycle 1, Day 1	Pre-dose and 1, 3 and 18-24 hours post-dose

[a.] Pre-dose within 10 minutes prior to dosing. Time allowance for samples 1 and 3 hours post-dose ± 15 minutes.

8.7 Human Biological Sample Biomarkers

8.7.1 Collection of Mandatory Samples for Biomarker Analysis

There is no additional biomarker sample collection in this study.

8.7.2 Other Study-related Biomarker Research

Already collected PK or PD samples may be analysed to explore potential biomarkers, which may influence the progression of NF1 and inoperable PNs (and associated clinical characteristics) and/or identify participants likely to respond to selumetinib or may be surrogate markers of response. Exploratory biomarker analyses may include (but not limited to) phosphorylated ERK, cytokines, and/or quantification of RNA expression using quantitative RT-PCR, microarray, or other technology in blood, peripheral blood mononuclear cells, serum, or plasma to evaluate their association with observed responses to selumetinib. This analysis excludes genomic analysis, but targeted sequence analysis on genes involved in NF1 might be included. This biomarker research is subject to additional optional consent in the ICF.

For storage, re use, and destruction of biomarkers samples, see Section 8.6.

8.8 Optional Genomics Initiative Sample

Not applicable.

8.9 Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

No formal hypotheses will be tested.

The primary PK objective of the study is to estimate the granule formulation single dose AUC0-12 for the final recommended dose schema in paediatric participants aged ≥ 4 to < 7 years and aged ≥ 1 to < 4 years and check the estimation with the capsule formulation single dose AUC0-12 at 25 mg/m^2 as observed in the pivotal safety and efficacy study SPRINT.

9.2 Sample Size Determination

Global Cohorts (Cohorts 1 and 2)

Approximately CCI participants will be dosed in Cohorts 1 and 2 to achieve CCI evaluable participants at the recommended granule formulation dose schema, of whom at least CCI participants will be aged ≥ 1 to < 4 years (with at least CCI aged < 2 years) and at least CCI participants will be aged ≥ 4 to < 7 years. A sample size of CCI participants will provide reasonable precision to characterise PK and safety.

At least CCI evaluable participants in each age group are required at the final recommended granule formulation dose schema.

With a minimum of CCI evaluable participants in each age group and CCI evaluable participants in total, the numbers of participants in the 2 age groups will fall between a combination of CCI to a combination of CCI With sample sizes of CCI in an age group, the power to show that the CCI% CI of the AUC_{0-12} geometric mean falls within the acceptance range CCI -fold of the SPRINT AUC_{0-12} geometric mean; FDA Guidance 2014) will be 90%, 99.9% and > 99.9%, respectively. The power for two age groups falling within the acceptance range simultaneously will therefore be 90% × 99.9% ≈ 90% and 99.9% × 99.9% ≈ 99.9% for the CCI combination and CCI combination, respectively. This sample size calculation assumes that there is a CCI% difference in exposure between the granule and capsule formulation and assumes an inter-subject gCV% of CCI% (Wang et al 2012). The choice of gCV% is based on observations from Study 89 (CCI%) and the SPRINT study (CCI%).

In the dose-finding phase of this study, the exposure AUC0-12 will be monitored on an ongoing basis. The minimum sample size for each cohort and the study may be re-estimated when CCI evaluable participants in that cohort have provided acceptable PK exposures. The re-estimation will use the observed inter-subject gCV%. Table 17 below shows the minimum sample sizes required in each age group corresponding to different variability and different scenarios.

Table 17 Sample Size Estimations based on Inter-subject gCV% and Expected Differences in AUC0-12 between SPRINKLE and SPRINT studies

Inter-subject gCV%	Difference in AUC0-12 between SPRINKLE and SPRINT studies		
	± 5%	± 10%	± 15%
CCI			

AUC_{0-12}, area under the concentration-time curve from time zero to 12 hours; CV, geometric coefficient of variation.

Japan Cohort

In addition to the Global Cohorts (Cohorts 1 and 2), a separate Japan Cohort of a minimum of CCI evaluable Japanese participants aged ≥ 1 to < 7 years will be recruited in Japan.

An evaluable participant for PK and sample size calculations is defined as a participant with a PK profile on Day 1 (for an individual at least 6 samples during the 12-hour time period post first dose on Cycle 1, Day 1 and must include the 10-12 hour PK sample) without any important protocol deviations potentially impacting the PK results.

Note: "Enrolled" means a participant's or their legally authorised representative (parent or guardian) and participant's (if deemed appropriate as per local regulations) agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not receive selumetinib, are considered "screen failures", unless otherwise specified by the CSP.

9.3 Populations for Analyses

The populations are defined as shown in Table 18.

Table 18 Populations for Analysis

Population/Analysis set	Description
All Enrolled	All participants who sign the ICF
Pharmacokinetic Analysis Set	All participants who receive at least one dose of selumetinib and who have at least one post-dose quantifiable plasma concentration with no important protocol deviations
Safety Analysis Set	All participants who receive at least one dose of selumetinib

ICF, informed consent form.

Note: The PK data for the Japan Cohort will be summarised separately to the PK data for the Global Cohorts.

In the case of an important protocol deviation or events that may impact the quality of the data, affected PK data collected will be excluded from the summaries and statistical analyses, but will

still be reported in the study result listings. Important deviations will be listed and summarised in the Clinical Study Report. The study physician, pharmacokineticist, and statistician will agree on the strategy for dealing with data affected by protocol deviations or events that may impact the quality of the data before any statistical analysis is performed.

9.4 Statistical Analyses

The Statistical Analysis Plan will be finalised prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1 General Considerations

All study data, originally captured or derived, will be listed and summarised as appropriate.

In the rest of this section, the planned analyses are general and will be performed both for Global Cohorts and Japan Cohort. If an analysis is particular for one population (for example the granule/capsule PK exposure comparison), it will be stated so.

The PK analysis will be based on the PK analysis set. Plasma concentrations and all PK parameters derived from plasma concentrations will be listed and summarised. In the case of an important protocol deviation or event, affected PK data may be excluded from the summaries and statistical analyses, but will still be included in the data listings. The PK exclusion decision will be documented by the PK scientist including the reason(s) for exclusion. PK analyses for the Japan Cohort will be presented separately from the Global Cohorts.

The safety analyses will be based on the safety analysis set. Continuous variables will be summarised using descriptive statistics (n, mean, SD, minimum, median, maximum). Categorical variables will be summarised in frequency tables (frequency and proportion). There are no statistical analyses other than summary statistics planned for safety endpoints.

Participant disposition will be presented for all enrolled participants. Protocol deviations will be discussed at the data review meeting before database lock and will focus on deviations from the CSP including (but not limited to):

- Inclusion/exclusion criteria deviations
- Dosing deviations
- Time window deviations for PK or safety assessments
- Receiving prohibited concomitant medications
- Other procedural and study conduct deviations

Efficacy evaluation will be based on the safety set using PN response data from volumetric MRI.

All statistical analyses and production of tables, figures and listings will be performed using

There will be 3 analysis time points:

1 Pharmacokinetic, dose-finding, and primary safety analysis:
   – A DCO (DCO1) and analysis will occur after all participants have had the opportunity to complete 3 cycles of treatment. This primary analysis will confirm the recommended granule formulation dose schema and assess PK, safety/tolerability and palatability. The timing of DCO1 may be different for the Global Cohorts (Cohorts 1 and 2) from the Japan Cohort, based on their date of Last Subject In.
   – The PK samples will be analysed on a regular basis to inform SRC. It is expected that single and multiple dose PK from all participants dosed with selumetinib would be available within 3 months of the last participant being dosed; at this point, all participants will have palatability data available and a minimum of 3 months of safety data.
2 Safety and efficacy of the granule formulation:
   – A DCO (DCO2) and analysis will occur after all participants in the study (Global and Japan Cohorts) have had the opportunity to complete 25 cycles (or terminated selumetinib); this analysis will provide additional PK and safety/tolerability data, as well as palatability and efficacy data.
   – Efficacy analyses will be performed, including: ORR (assessed by ICR and investigator), CCI and COAs.
3 Long term safety follow-up for participants until they reach the age of 5 years or commence an alternative systemic NF1-PN treatment, whichever is the earlier:
   – A final analysis will occur when all participants in the study (Global and Japan Cohorts) have had the opportunity to complete their last assessment in the study, including the safety follow-up for participants aged < 5 years.
   – All of the safety/tolerability analyses will be updated with the data captured after the DCO for the analysis shown in bullet point 2 above (safety and efficacy of the granule formulation).

9.4.2 Pharmacokinetic Assessments

9.4.2.1 Primary and Secondary Endpoint(s)

Pharmacokinetic parameters will be derived for selumetinib using plasma concentrations.

Selumetinib PK is not time-dependent and minimal accumulation was observed in adult or paediatric participants following chronic bid dosing. In addition, sample size calculations have been based on single dose PK variability from Study 89. Therefore, single dose AUC0-12 will be used as the primary PK variable for comparison with SPRINT data.

Summary statistics including gCV%, arithmetic mean (SD), median (min, max) will be provided by age and BSA group. The geometric mean is calculated as the exponential of the arithmetic mean

calculated using log-transformed data. The gCV% is calculated as $100\sqrt{\exp(s^2)-1}$ where s is the SD of the log-transformed data.

At the final sample size for the recommended dose schema in the Global Cohorts (Cohorts 1 and 2), the AUC0-12 geometric mean and [redacted]% CI (from one sample t-statistic) will be determined for each age group and overall. If the [redacted]% CI falls within [redacted]% of the geometric mean AUC0-12 observed in the pivotal safety and efficacy study, SPRINT, then it will be concluded that comparable exposure to selumetinib was observed across the age groups.

Box and whisker plots of observed AUC0-12 will be produced for comparison to the target range for the capsule formulation determined from SPRINT.

9.4.2.2 Secondary Endpoint(s)

Pharmacokinetic parameters will be derived for selumetinib and N-desmethyl selumetinib using plasma concentrations.

The following secondary PK parameters will be calculated, if appropriate, and if data allow:

- Plasma concentrations and PK parameters of selumetinib including, but not limited to:
  - AUC0-12 derived after multiple dose administration.
  - Cmax, AUC0-6, AUClast, CL/F, tmax, tlast; derived after single and multiple dose administration.
  - AUC0-24, Vz/F and t½λz after single dose administration.
  - Rac Cmax, Rac AUC0-12, and Vss/F derived after multiple dose administration.
- Plasma concentrations and PK parameters of N-desmethyl selumetinib, including, but not limited to:
  - Cmax, AUC0-6, AUC0-12, AUClast, tmax, tlast derived after single and multiple dose administration.
  - Rac Cmax and Rac AUC derived after multiple dose administration.
  - Parent-to-metabolite ratio for AUC0-6, AUC0-12 and AUC0-24 (single dose only) and Cmax derived after single and multiple dose administration.

For the participants that transition to capsule formulation BSA normalised AUC0-6, AUC0-12, AUClast and Cmax will be determined following multiple dose administration of granule and capsule formulation. The ratio of granule:capsule formulation will be determined for each of these parameters, the data will be listed and summarised.

Summary statistics including geometric mean (geometric CV%), arithmetic mean (SD), median (min, max) will be provided by formulation, analyte and period for AUC0-6, AUC0-12, AUC0-24, AUClast and Cmax. For CL/F, Rac Cmax, Rac AUC0-12 and for the comparisons of BSA normalised PK parameters for capsule and granule only arithmetic mean (SD) and median (min,

max) will be presented. For tmax and tlast, only median (min, max) will be presented. For CL/F, t½λz, Vss/F and Vz/F only arithmetic mean (SD) and median (min, max) will be presented.

Selumetinib and N-desmethyl selumetinib plasma concentrations and PK parameters will be listed and summarised by formulation, age group, dose group and BSA group for Cycle 1 Day 1, Cycle 2 Day 1 and capsule dosing Day 7 (range Day 4 to 14).

Geometric mean (± geometric SD) plasma concentration versus nominal sampling time will be plotted in a linear and semi-logarithmic scale for each PK sampling period and with a separate plot for each analyte. Exploratory analyses may be conducted to explore the relationship between exposure or PK parameters, PBPK simulations and the pharmaceutical properties of the API and/or the formulation.

Box and whisker plots of observed PK parameters will be produced for comparison to the target range for the capsule formulation determined from SPRINT.

Further data presentation and reporting details will be provided in the Statistical Analysis Plan.

Details of CCI analyses will be described in the CCI finalised before database lock. The CCI analyses will be presented separately from the main Clinical Study Report.

9.4.2.3 Exploratory Analyses

Exploratory analyses may be conducted, for example, using CCI and on the CCI of the CCI and/or the CCI.

9.4.3 Safety

9.4.3.1 Primary Endpoint(s)

Safety and tolerability will be evaluated in terms of AEs, palatability, clinical safety laboratory assessments, physical examination, weight, vital signs, ECG, ECHO, ophthalmologic assessment, knee (or wrist) MRI/X-ray, and performance status.

All safety assessments will be listed.

All AEs will be coded using MedDRA. A treatment emergent AE is defined as an AE which starts, or worsens, after the first dose of study drug. Treatment-emergent AEs will be summarised including tabulations by causality and severity. All tabulations will be presented by system organ class and preferred term. Serious AEs and AEs leading to treatment discontinuation will be listed separately.

For laboratory assessments, weight, vital signs, physical examination, ECG, ECHO, ophthalmologic assessment, knee (or wrist) MRI/X-ray, and performance status, summary statistics will be provided as appropriate. Continuous variables will be summarised by number, mean, SD, minimum, median, maximum. Categorical variables will be summarised in frequency tables (frequency and proportion). Only descriptive statistics are planned for safety endpoints.

For haematology and clinical chemistry, changes from baseline will also be presented in summary tables. Grade shift tables (from baseline to maximum on treatment) will also be presented. Change from baseline or grade shift may also be provided for other safety assessments if appropriate.

9.4.3.2 Exploratory Safety Endpoints

Exploratory safety endpoints include CCI and the CCI All data will be listed by visit. Continuous variables will be summarised by number, mean, SD, minimum, median, maximum. Categorical variables will be summarised in frequency tables (frequency and proportion).

9.4.4 Efficacy Endpoints

Efficacy endpoints include PN responses from volumetric MRI and COAs. Plexiform neurofibroma responses from on-treatment MRI scans will be considered as primary estimands and responses from all MRI scans (regardless of treatment discontinuation) will be considered as supplementary estimands.

Efficacy analysis will be conducted on the safety set for ORR; CCI , and COAs as defined in Section 8.1. For all efficacy analysis, missing data will not be imputed (will be treated as missing or censored).

9.4.4.1 Secondary Efficacy Endpoint

Objective response rate is a secondary endpoint which will be estimated together with 95% CIs constructed using the Clopper-Pearson method (Clopper and Pearson 1934).

9.4.4.2 Exploratory Efficacy Endpoints

CCI are exploratory endpoints. Median and 95% CI will be calculated using CCI will be provided for each of these endpoints.

The following COAs are exploratory endpoints which will be summarised for the Safety Set:

- CCI
-
-
-
-
-

CCI will be provided if appropriate.

9.4.5 Other Analyses

Demographic and disposition data, as well as exposure data, will be listed and summarised. The exposure summary will include duration of treatment (total and actual) and treatment interruptions in each treatment period. Demographic and exposure data will be presented using the Safety

Analysis Set. Disposition data will be presented for all enrolled participants.

Prior and concomitant medications will be listed for the Safety Analysis Set.

Compliance with questionnaires completed by parent/guardian or participant will be summarised as appropriate; details will be provided in the Statistical Analysis Plan.

pERK inhibition in PBMCs will be summarized by scheduled sample time points and change from pre-dose for the subset of participants who provide pERK samples.

Biomarker exploratory analyses will be described in a separate analysis plan and will be reported outside the Clinical Study Report in a separate report. The results of this biomarker assessment will be reported as an addendum, and/or separately in a scientific report or publication. The results of this biomarker assessment may be pooled with biomarker data from other studies with the study intervention to generate hypotheses to be tested in future research.

9.5 Interim Analyses

There is no interim analysis planned for this study.

9.6 Data Monitoring Committee

Not applicable.

Safety Review Committee

An SRC will be formed for the dose-finding phase to evaluate the safety, tolerability and PK data of the granule formulation dose schema for selumetinib. Section 6.1.2 provides information on SRC reviews and decision points. Detailed information will be provided in the SRC charter.

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 CSP and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and CIOMS International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, revised protocol, ICF, Investigator Brochure, and other relevant documents (eg, 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 revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with AstraZeneca.
- The Investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to AstraZeneca of an 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.
- AstraZeneca 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. AstraZeneca 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 SUSAR according to local regulatory requirements and sponsor policy and forwarded to Investigators as necessary.
- Adherence to European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then

file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

Prompt notification by the Investigator to AstraZeneca of any (potential) serious breach of the protocol or regulations is essential so that legal obligations and ethical obligations are met.

- A "serious breach" means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical trial.

AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and Investigators.

- Where the EU Clinical Trials Regulation 536/2014 applies, AstraZeneca has in place processes to enter details of serious breaches into the European Medicines Agency CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.

If any (potential) serious breach occurs in the course of the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after they become aware of it.

In certain regions/countries, AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.

The Investigator should have a process in place to ensure that:

- The site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach.
- A (potential) serious breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

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 also responsible for providing information on financial interests during the course of the study and for one year after completion of the study.

A 3 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and his/her legally authorised representative (parent/guardian) and answer all questions regarding the study.
- The participant's legally authorised representative (defined as parent or guardian) and participant (if deemed appropriate per local regulation) must be informed that their participation is voluntary and they are free to refuse to participate and may withdraw their

consent at any time and for any reason during the study. The participant's legally authorised representative (defined as parent or guardian) and participant (if deemed appropriate as per local 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 (HIPAA) requirements, where applicable, and the IRB/IEC or study centre. Participants may also be required to sign a statement of assent if deemed appropriate as per local regulations.

- The medical record must include a statement that written informed consent was obtained before the participant 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.
- The participant's legally authorised representative and participant (if deemed appropriate as per local regulations) must be re-consented to the most current version of the ICF/assent during their participation in the study.
- A copy of the ICF/assent must be provided to the participant's legally authorised representative and participant (if deemed appropriate as per local regulations).

In cases where a participant is rescreened, another ICF is not required to be signed if the rescreening occurs within 28 days from the previous ICF signature date.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological samples. The Investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use and may withdraw their consent at any time and for any reason during the retention period.

A 4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) in the informed consent.
- The participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) must be informed that the participant's 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.

- The participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) must be informed that data will be collected only for the business needs. We will only collect and use the minimum amount of personal data to support our business activities and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.
- The participant's legally authorised representative (parent or guardian) and participant (if deemed appropriate as per local regulations) must be informed that in some cases their data may be pseudonymised. The General data Protection Regulation (GDPR) defines pseudonymisation as the processing of personal data in such a way that the personal data can no longer be attributed to a specific individual without the use of additional information, provided that such additional information is kept separately and protected by technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches it is important that investigators that work with AstraZeneca have controls in place to protect patient data privacy.

The Investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

[1] The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal Data Breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or Principal Investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (i.e., Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or Principal Investigator, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in

relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 5 Committees Structure

N/A

A 6 Dissemination of Clinical Study Data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons, as otherwise statistical analysis is not relevant.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com, http://www.clinicaltrials.gov and https://euclinicaltrials.eu/ as will the summary of the main D1346C00004 study results when they are available. The clinical study and/or summary of main D1346C00004 study results may also be available on other websites according to the regulations of the countries in which the main D1346C00004 study is conducted.

A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by 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.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- 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 participants are being protected; and that the study is

being conducted in accordance with the currently approved CSP 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 a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. 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 participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data entered in 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.
- Definition of what constitutes source data can be found in the Trial Master File and Investigator Site File.

A 9 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first participant screened is considered the first act of recruitment and will be the study start date.

The sponsor 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. 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 CSP, 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

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CROs used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. All data available for the participant at the time of discontinuation must be recorded in the eCRF together with the reason for the discontinuation.

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 Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a patient or clinical study participant 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 (eg, an abnormal laboratory finding), symptom (eg, 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 non-serious 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 intervention has been administered.

B 2 Definition of Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires in-participant 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 participant or may require medical treatment to prevent one of the outcomes listed above.

Life-threatening

'Life-threatening' means that the participant 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 participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself an SAE, although the reasons for it may be (eg, 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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

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 participant 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.

- Angioedema not severe enough to require intubation but requiring IV 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 (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

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 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). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 3 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 participant 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 rechallenge.
- 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 no available facts or arguments to suggest a causal relationship, 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 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca NIMP 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, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route, dose (error greater than ± 10%) or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

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

- Errors related to or resulting from IRT/RTSM - 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), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

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

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP/study intervention or AstraZeneca NIMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP/study intervention or AstraZeneca NIMP for medicinal purposes outside of the authorised product

information, or for unauthorised IMPs/study interventions or AstraZeneca NIMPs, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

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

The Investigator at each centre keeps full traceability of collected biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing information related to the samples whilst at site.

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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives 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.

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 required, AstraZeneca will ensure that remaining biological samples are returned to the site or destroyed at the end of the retention period as described in the informed consent.

If the participant's legally authorised representative (parent or guardian) and/or participant (if deemed appropriate as per local regulations) withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures the participant's legally authorised representative (parent or guardian) and/or participant's (if deemed appropriate as per local regulations) withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures the participant's legally authorised representative (parent or guardian) and/or participant (if deemed appropriate as per local regulations) and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn

consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site is notified.

C 3 International Airline Transportation Association 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN 3373 and IATA 650

Exempt - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- 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 (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

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 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 participant 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 TBL 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. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI 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

Potential Hy's Law

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

Hy's Law

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, 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 TBL, but there is no specified timeframe within which the elevations in transaminases and TBL 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 participant who meets any of the following identification criteria in isolation or in combination:

- Alanine aminotransferase ≥ 3 × ULN
- Aspartate aminotransferase ≥ 3 × ULN
- Total bilirubin ≥ 2 × ULN

Local Laboratories:

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 participant meets PHL criteria (see Section 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 participant does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the participant 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 participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within one 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 participants 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 participant's condition.
- The Medical Monitor contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:

- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Medical Monitor.
- Complete the three 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 TBL) 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 Medical Monitor 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 Medical Monitor contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was 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 TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a 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 TBL 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.

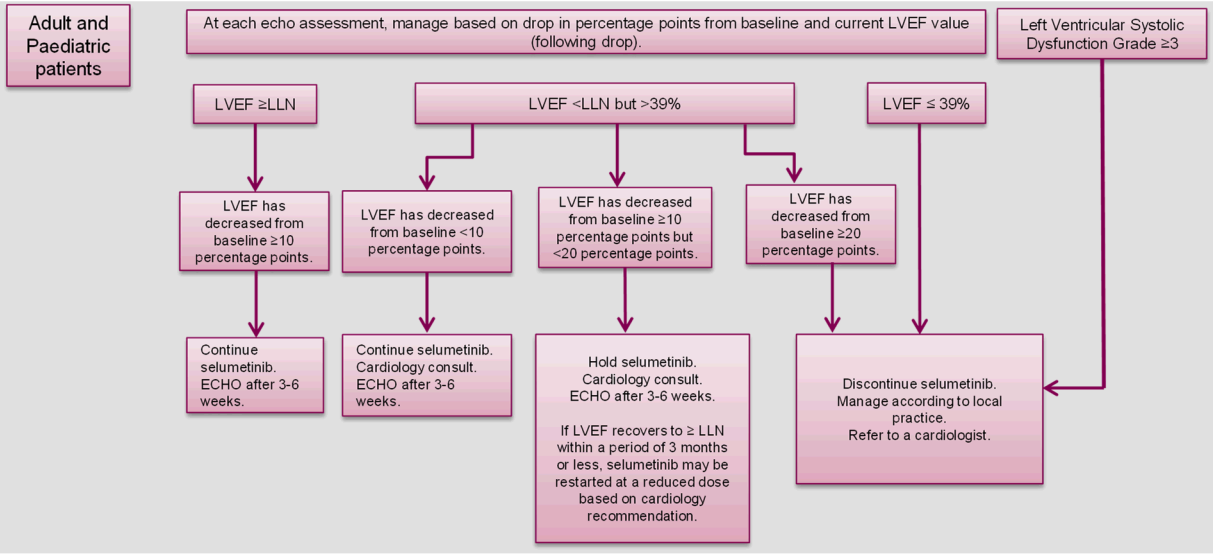
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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 PHL (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria 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.

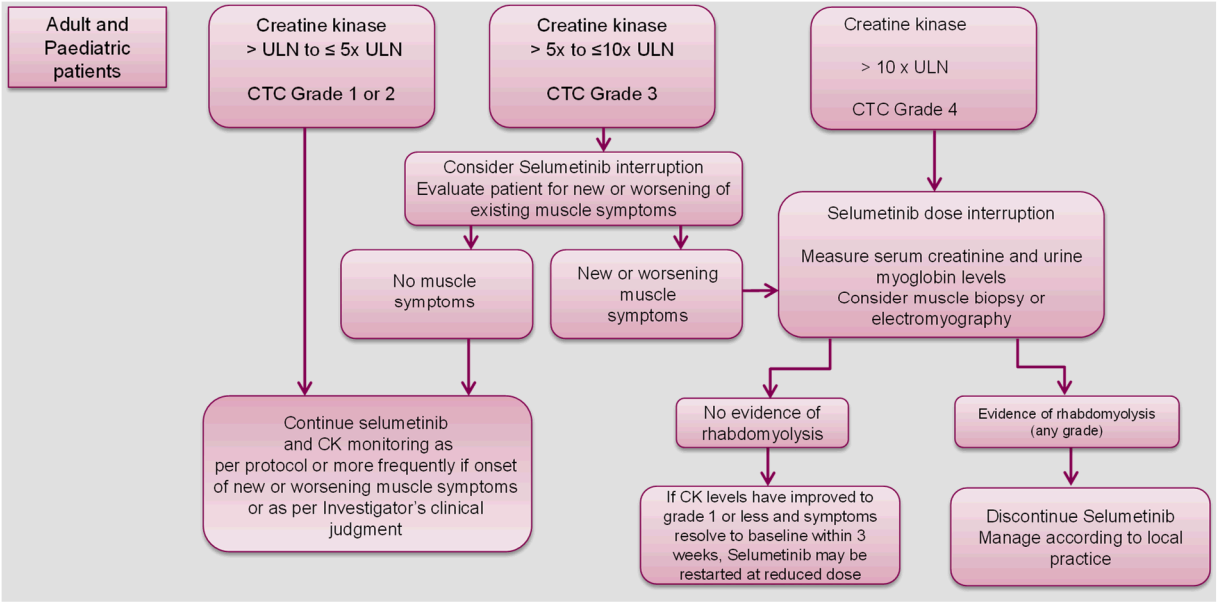
Appendix E Guidance for Management of Specific Adverse Events

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



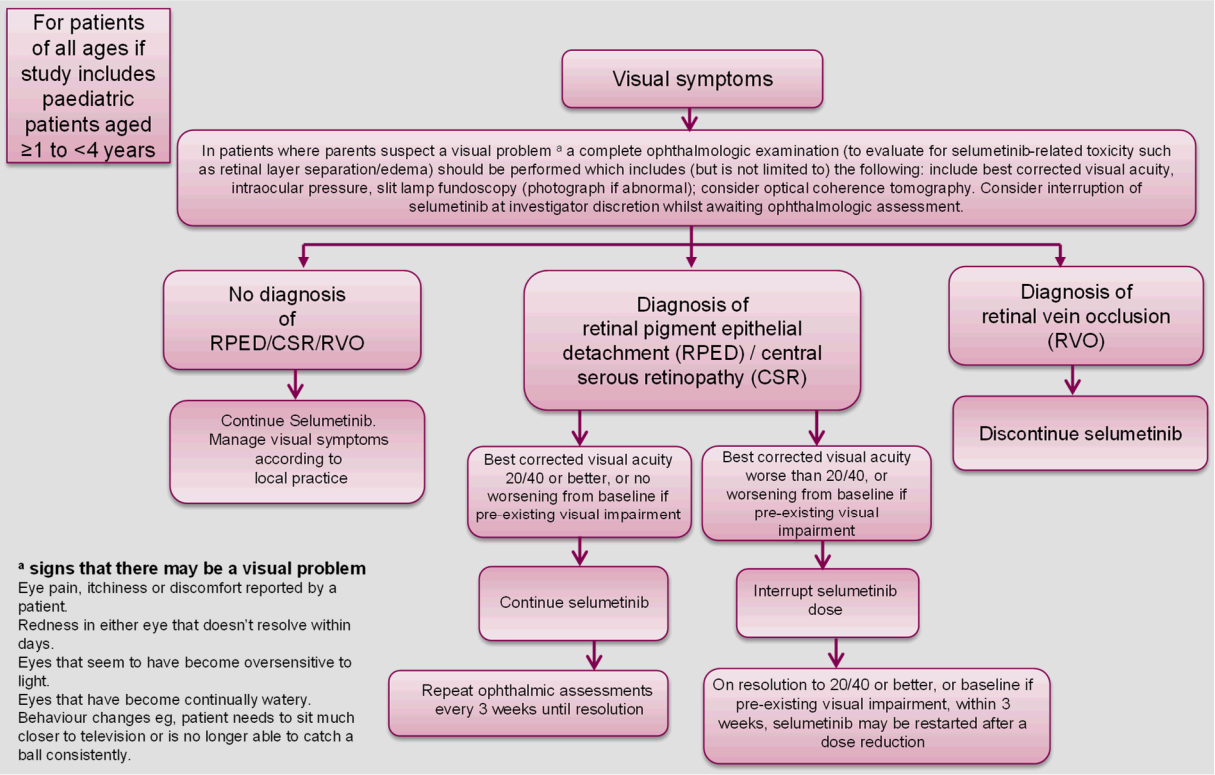
ECHO, echocardiogram; LLN, lower limit of normal per local institution or site; LVEF, left ventricular ejection fraction.

E 2 Management of Creatine Kinase Elevation



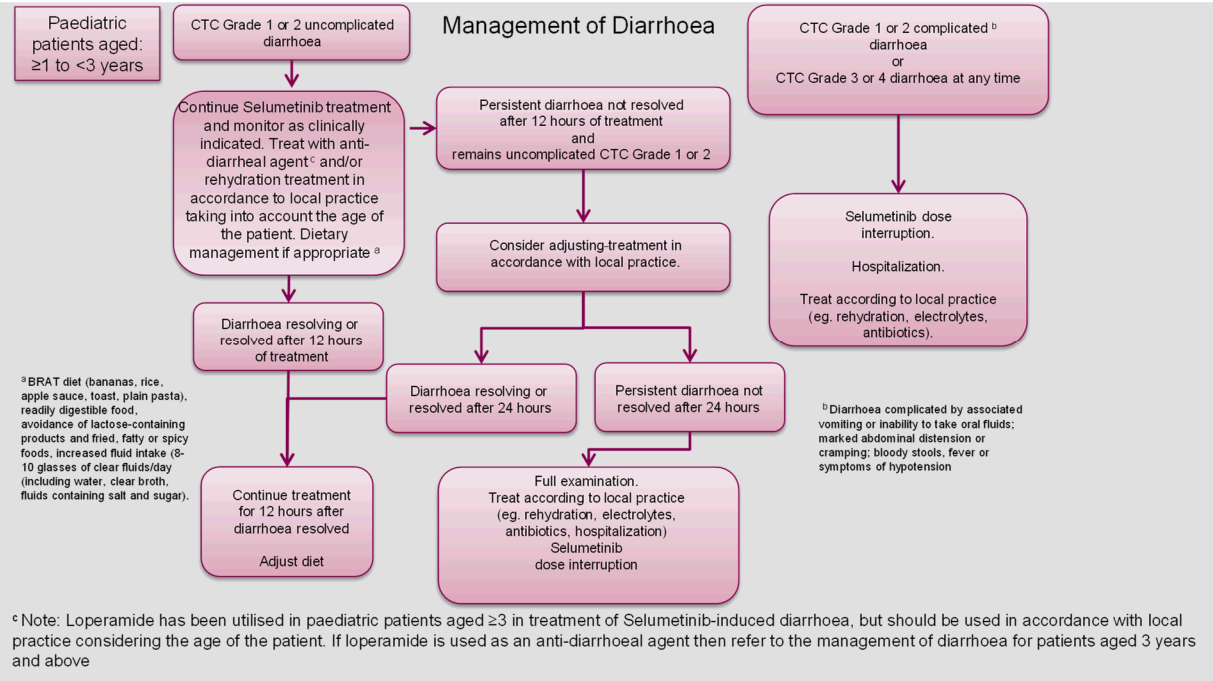
CK, creatine kinase; CTC Common Terminology Criteria for Adverse Events

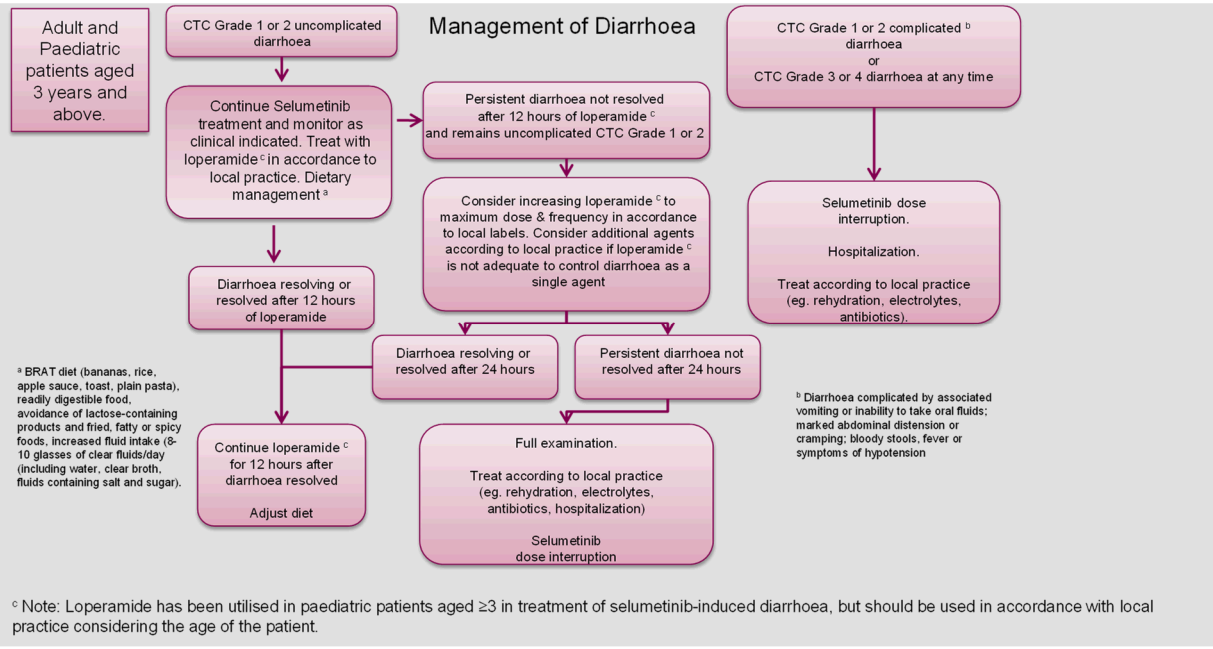
E 3 Management of Retinal Pigment Epithelial Detachment, Central Serous Retinopathy and Retinal Vein Occlusion



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

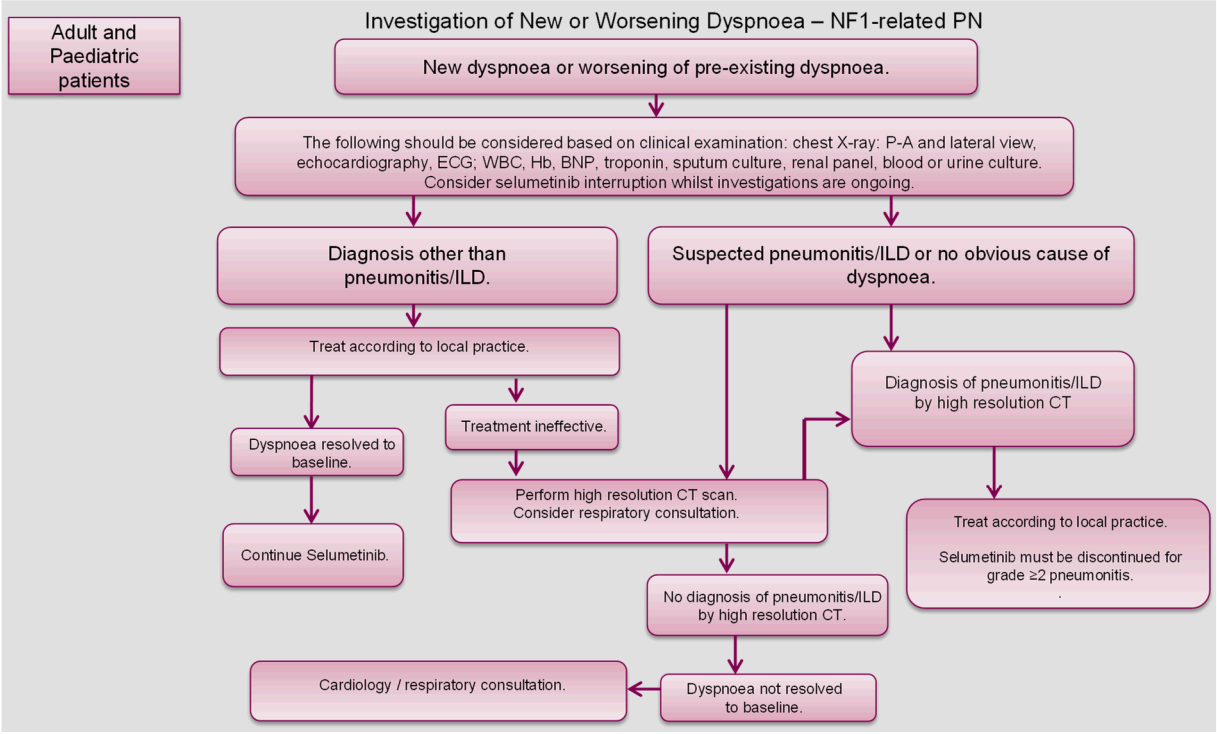
E 4 Management of Diarrhoea





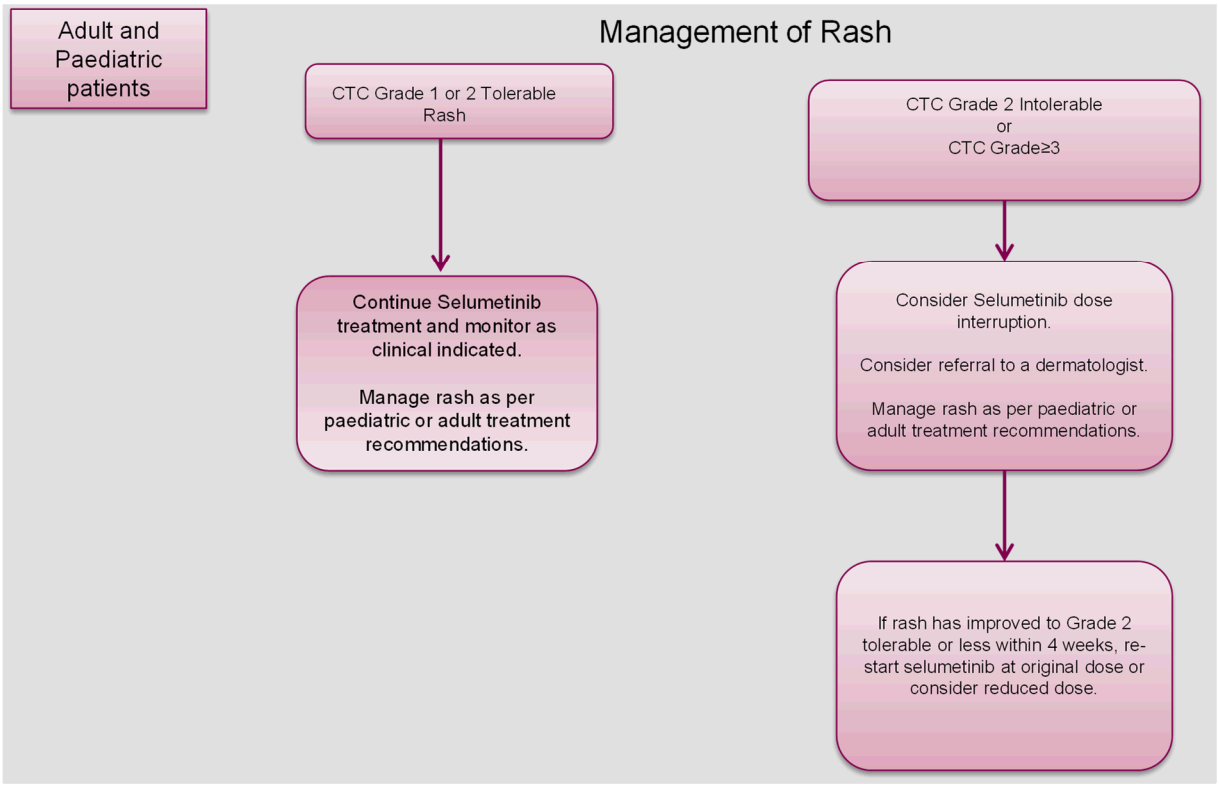
CTC. Common Terminology Criteria for Adverse Events

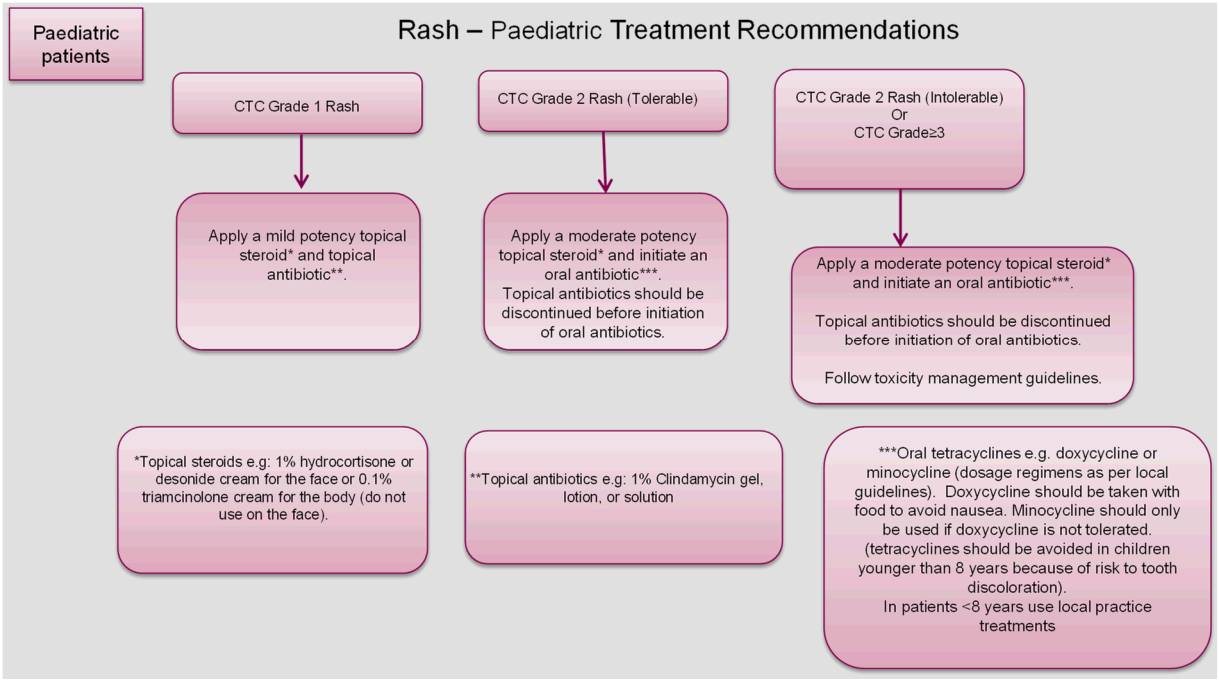
E 5 Management of New or Worsening Dyspnoea



BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; Hb, haemoglobin; ILD, interstitial lung disease; NF1, neurofibromatosis type 1; P-A, posterior-anterior, PN, plexiform neurofibroma; WBC, white blood cell

E 6 Management of Participants with Rash



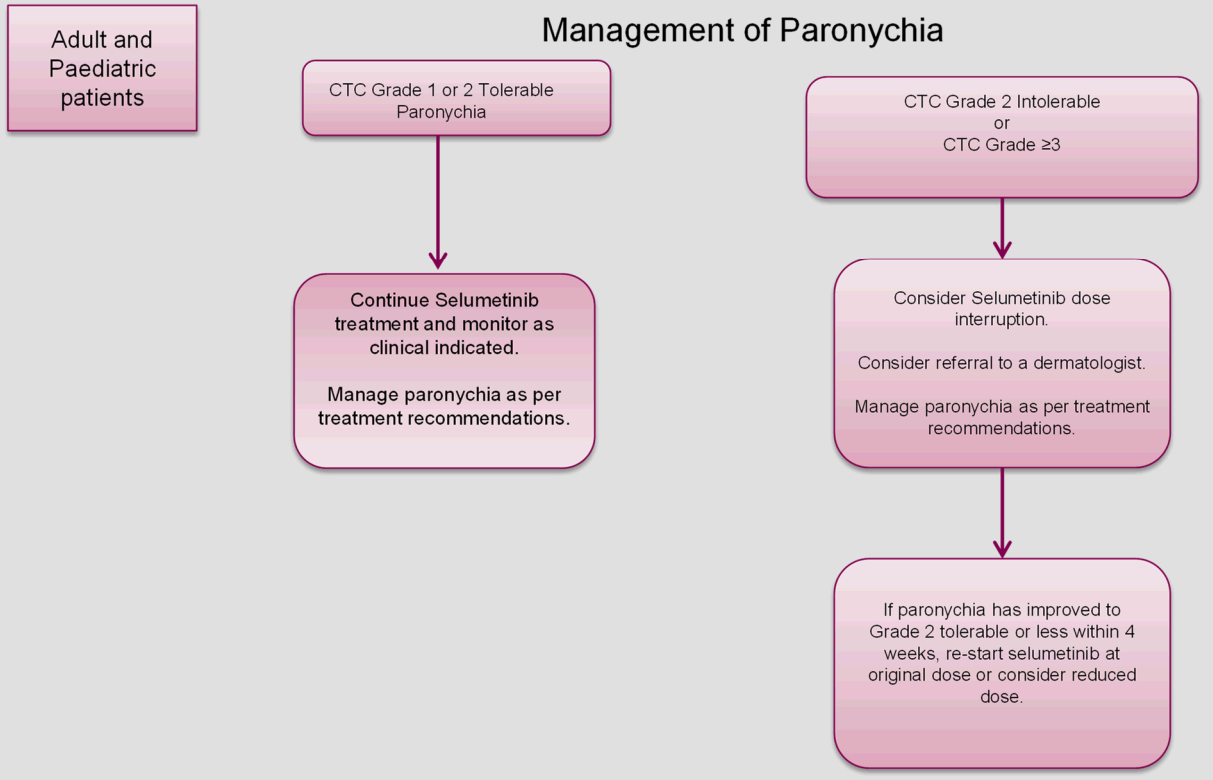


E 7 Oral Care Management for Events of Oral Mucositis and Dry Mouth

Oral care guidelines 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 if possible.
- 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



CTC, Common Terminology Criteria for Adverse Events

E 9 Paronychia Treatment Recommendations

Adverse event	Treatment recommendations
Paronychia*	**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.

CTCAE, Common Terminology Criteria for Adverse Events

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 F19 Blood Pressure Levels for Children by Age and Height Percentile – Blood Pressure for Boys

Age years	BP percentile	Systolic BP (mmHg)							Diastolic BP (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 F20 Blood Pressure Levels for Children by Age and Height Percentile – Blood Pressure for Girls

Age years	BP percentile	Systolic BP (mmHg)							Diastolic BP (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 F21 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 left ventricular dysfunction).	> 7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or angina pectoris (mild congestive heart failure).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate congestive heart failure).	2 to 3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of congestive heart failure present at rest (severe congestive heart failure).	1.6

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.
VO2, maximal oxygen uptake.

Appendix G Country-specific Requirements

OVERALL RATIONALE FOR THE ADDENDUM VERSION 6 (GERMANY):

Reason: To collect wet-ink signatures from the sponsor and national coordinating investigator for CSP Version 4.0, dated 14 February 2023 and to describe further changes in the CSP.

Section # and Name	Description of Change with Reason
Section 1, Protocol summary; Section 1.3, Schedule of Activities (Table 2 and 3); Section 2.3.1, Risk assessment (Table 4); Section 3, Objectives and Endpoints (Table 5); Section 8.2.7, Knee/Wrist MRI/X-ray; Section 9.4.3.1, Primary Endpoints	To assess the safety and tolerability of the selumetinib granule formulation (physeal dysplasia) just MRI scans will be used. X-ray scans will not be performed in Germany to reduce the patient burden. Those MRI scans can be performed in parallel to the PN assessments and there will be no risk of radiation for the patients.
Section 4.1.1, Study Conduct Mitigation during	This Section provides guidance during cases of civil crisis, natural disaster, or public health crisis. We specify that in Germany:

<table>
<tr><th>Section # and Name</th><th>Description of Change with Reason</th></tr>
<tr><td>Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health; Appendix J, Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis</td><td>• The extent of the actions is restricted to the COVID-19 pandemic
• Duties overseen by the PI will not be delegated to Health Care Providers (HCP)/Third Party Vendors (TPV)
• The PI or sub-investigators are responsible for the procedures such as performing blood draws, measuring vital signs, weight or height</td></tr>
<tr><td>Section 8.3.9, Reporting of Serious Adverse Events</td><td>With respect to SAE reporting described in this section, we clarify that the timespans (no later than 24 hours) do not apply. In Germany, SAE reporting has to be done immediately without undue delay after obtaining knowledge. Sites will be accordingly trained as per standard for clinical trial in Germany.</td></tr>
<tr><td>Section 1.3, Schedule of Activities; Section 8.1, Efficacy Assessments; Section 8.2.9, Clinical Safety Laboratory Assessments; Section 8.5, Human Biological samples</td><td>AstraZeneca has considered the burden on the study participants throughout the study design process. As requested by EC, summarised below is the patient burden caused by blood draws and MRI scans that should be minimal in this patient population.

In order to ensure the total blood volumes collected are appropriate for this patient population, AstraZeneca have referred to the European condition requirements.
The pharmacokinetic sample volume for each timepoint has been reduced in comparison to the previous adult studies considering the paediatric population.

With reference to the Blood Volume Guidelines V1.1, November 30, 2015, Stellenbosch University, Health Research Ethics Committee, the minimum BSA for inclusion in this study is 0.4m^2, which equates to a weight of 7.5kg, it is therefore expected that these patients have a total blood volume of 560mL. As such, per the guideline, 5% (28mL) of total blood volume can be taken in a one-off sampling, and within a 3 month time period. The first three months of the study include the most intensive sampling, in this period of time 14.0mL of blood will be taken which is lower than the maximum that can be taken per the guidance.
Additionally, in patients ≥27Kg, optional pharmacodynamic samples can be taken. It is expected that these patients have a total blood volume of 2080mL, 5% of their total blood volume is therefore 104mL. Within the first 3 months of the study, 30.0mL of blood will be taken, which is lower than the maximum that can be taken per the guidance. AstraZeneca therefore confirm that the planned blood draws are within the Stellenbosch University, Health Research Ethics Committee guidance.

Blood volumes planned to be taken within the first 3 months (most intensive period) of the SPRINKLE study
<table>
<tr><th></th><th>Number of Timepoints</th><th>Volume per timepoint</th><th>Total Blood volume</th></tr>
<tr><td>Clinical chemistry & Haematology[1]</td><td>5</td><td>1.0mL</td><td>5mL</td></tr>
</table>
</td></tr>
</table>

Section # and Name	Description of Change with Reason

	(Screening, cycle 1 day 1, cycle 1 day 15, cycle 2 day 1, cycle 3 day1)		
Troponin[1]	1 (Screening)	0.5	0.5mL
Pharmacokinetics	17 (9 on cycle 1 day 1, 8 on cycle 2 day 1)	0.5mL	8.5mL
Pharmacodynamics[2]	4 (Cycle 1 Day 1)	4.0mL	16.0mL
		Total in first 3 months of study ***Patients <27kg or ≥27Kg and don't provide optional PD samples***	14.0mL
		Total in first 3 months of study ***Patients ≥27Kg only that provide optional PD samples***	30.0mL

[1]*Safety samples are performed by local lab, therefore actual volumes will vary depending on the Institution. Each site is advised to minimise the amount of blood required.*

[2]*Optional pharmacodynamic samples which are collected only in patients ≥27Kg.*

Investigators participating in the SPRINKLE study will use their discretion in the method of collecting biological samples to ensure that it is the least invasive manner for their patient. To minimise the number of punctures, the schedule of assessments is designed so that safety and PK samples can be taken at the same timepoint. PK samples can be taken using venous catheter to minimise the number of punctures, and AstraZeneca recommends that this is the approach Investigators use in order to minimise burden on the patient. Additionally sites are advised to use local measures such as local anaesthesia to reduce the discomfort of the blood sampling.

The intensive PK days of Cycle 1 Day 1, and Cycle 2 Day 1 require 9, and 8 samples respectively to be taken within a 24 hour period. This number of samples is required so that we can estimate the pharmacokinetic profile and obtain the AUC values which is a primary objective of the study. On intensive PK sampling days, participants aged ≥ 1 to < 4 years can take selumetinib granules with or without food, but participants aged ≥ 4 to < 7 years are required to take selumetinib granules on an empty stomach. The flexibility for the younger children may lead to variability in the Cmax and tmax as food intake is known to reduce the rate of absorption of selumetinib. Adequate numbers of samples are therefore required to capture the tmax of the plasma concentrations under these differing conditions. The final statistical analysis will compare the SPRINKLE study AUC0-12 (patients aged PPD to PPD years) to the SPRINT study AUC0-12 (patients aged PPD to PPD years) at the approved dose of 25 mg/m^2, and reducing the number of samples further could potentially lead to an underestimation of exposure which could compromise the study endpoint.

Section # and Name	Description of Change with Reason
	Patients must remain on the granule formulation until after they have completed their third cycle of treatment. Transition to the capsule formulation is encouraged in patients once they attain a BSA between 1.10 and 1.29 m^2 because a large number of the available granule formulation strengths would be required to achieve the dosage. In patients that transition from granule formulation to capsule formulation, an additional intensive PK sampling day will be conducted on Day 7 of the capsule formulation. (PK samples may be taken between Day 4 and 14 if twice daily dosing has been maintained for 3 days prior to the PK sample day, to allow flexibility). The intensive PK sampling on transition to capsule formulation requires 6 samples to be taken, in total approximately 3mL blood. The timepoints have been designed based on the known pharmacokinetic profile of the capsule formulation to ensure adequate samples are collected to calculate the PK parameters. There are MRIs planned for both assessments of PN volume and monitoring for physeal dysplasia. All assessments of physeal dysplasia monitoring are scheduled at the same time as those for PN volume to minimise the patient burden. As such, per the schedule of assessments there will be MRIs every 4 cycles in the first year, and every 6 cycles in the second year. In total there will be a maximum of 7 MRI assessments per patient. When receiving an alternative medical therapy for NF1-PN, MRI assessments in Germany could be conducted as often as every 3 months as standard of care. Therefore, the MRI assessment schedule implemented in SPRINKLE is in line, or slightly less burden than these patients would experience if receiving an alternative therapy. The requirement for sedation or anaesthesia during the MRI will be determined by the treating Investigator based on the patient and done according with standard of care, in line with best practice. Efficacy (Objective response rate) is a secondary endpoint, as required by the EMA Paediatric investigational plan. Additionally, time to response, duration of response, time to progression and progression free survival are exploratory endpoints. Therefore, in order to detect a confirmed response, or a progression it is important to conduct regular MRI scans. In the pivotal SPRINT Phase II Stratum 1 trial (patients aged PPD years old), 42.4% (14/33) patients had onset of response by 4 cycles from first dose, and 97.0% (32/33) had onset of response by12 cycles. It is therefore expected that the majority of patients who have confirmed response in the SPRINKLE study, will demonstrate initial response within the first year of treatment. The proposed MRI scheduling (every 4 cycles in the first year, followed by every 6 cycles in the second year) balances the ability to characterise time to onset of response, demonstrate confirmation of a response with 2 consecutive MRI scans within a 2 year treatment period, whilst being mindful of patient burden. Additionally, a more frequent schedule during this first year is important for the treating Investigator to determine that the patient is receiving clinical benefit and should continue receiving selumetinib treatment. The SPRINKLE study is based on a PK extrapolation strategy, whereby the extrapolated efficacy of the granule formulation will primarily be based on the observed selumetinib PK (exposure) matching that observed in the pivotal safety and efficacy study SPRINT (Gross et al 2020). The PK extrapolation approach uses fewer patients than a traditional Phase II or Phase III study design.

Section # and Name	Description of Change with Reason
	AstraZeneca and the SPRINKLE study PIs are committed to minimising the patient burden of participating in this study. Participation in this study does have an increased assessment burden, due to the necessary collection of pharmacokinetic samples mainly at the start of the study. However, participation in this study enables patients as young as 1 year-old with NF1 and symptomatic, inoperable PNs to receive treatment with an age-appropriate formulation of selumetinib without the need to fast instead of the capsule that requires fasting twice a day. This reduces the burden and duration of time for these young children to learn to swallow capsules whilst their PNs continue to grow and impact on their daily life. There is no alternative approved treatment for patients with NF1 and symptomatic inoperable PN who cannot swallow capsules.
Section 1.3, Schedule of Activities; Section 8.2.9, Clinical Safety Laboratory Assessments; Section 8.5, Human Biological samples	As requested by EC, it must be specified whether the mentioned number of 35ml blood includes only the pharmacokinetic samples or the necessary safety laboratory as well. The total amount of blood to be taken in the course of study (35mL) includes the planned safety laboratory samples as well as the pharmacokinetic tests that all patients will have. This does not include the optional pharmacodynamic samples that can only be collected in patients ≥27kg (See Section 8.5.2 of the CSP) or the pharmacokinetic samples that are collected only in patients if they transition from the granule to the capsule formulation (see section 8.5.1 of the CSP).
Section 1.1, Synopsis; Section 6.7, Intervention after the End of the Study	As requested by the EC, we changed the wording in the synopsis to describe the follow-up treatment more precisely. If selumetinib (capsule or granule formulation) is approved locally and reimbursed for use in paediatric patients with NF1 who have symptomatic, inoperable PN, participants should be switched to the commercial supply at the end of their participation in the study. However, if the participant is unable to access the commercial supply of selumetinib, and they are still receiving clinical benefit AstraZeneca and the investigator will ensure that the participant will be able to continue to receive selumetinib (capsule and granule formulation) if he/she is benefiting from treatment.

Appendix H Performance Status Scales

Table H22 Performance Status Criteria

Lansky Performance Status	
Score	**Description**
100	Fully active, normal.
90	Minor restrictions in physically strenuous activity.
80	Active, but tires more quickly.
70	Both greater restriction of and less time spent in play activity.
60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Mostly in bed; participates in quiet activities.
30	In bed; needs assistance even for quiet play.
20	Often sleeping; play entirely limited to very passive activities.
10	No play; does not get out of bed.

Lansky performance scores are intended to be multiples of 10.

Appendix I Guidance Regarding Potential Interactions with Concomitant Medications

Throughout the study, participants should avoid changes to, or the addition of all concomitant medications, in particular any that may affect the metabolism of selumetinib (eg, CYP2C19 or CYP3A4 moderate/strong inhibitors/inducers), unless considered clinically indicated.

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 s**hould be avoided until after the PK assessment on Cycle 2, Day 1. During the remainder of the study, if concomitant use of selumetinib with strong or moderate CYP3A4 and CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced by 20% as shown as an example for the granule formulation in Table I23 (note that the table uses the initial proposed dose for the selumetinib granule formulation; since the dose may be adjusted based on emerging safety, tolerability and PK data, the table may not include all scenarios). An example table for capsule dose reduction is shown in Table I24. The dose should be reduced for the duration of concomitant therapy with the strong or moderate CYP3A4 and CYP2C19 inhibitor and for 5 half-lives afterwards. After the washout of the inhibitor is complete, the selumetinib dose can be re-escalated. The participant should be monitored closely for potential toxicities. If a participant has had a dose reduction, or the granule dose is not included in the table, Investigators may contact the AstraZeneca Medical Monitor for advice.

In vitro selumetinib is an inhibitor of OAT3. The potential for a clinically relevant effect on the PK of concomitantly administered substrates of OAT3 (eg, methotrexate or furosemide) cannot be excluded and they should be given with caution.

Table I23 Recommended Granule Dosage of Selumetinib for Co-administration with Strong or Moderate CYP3A4 and CYP2C19 Inhibitors based on the Initial Proposed Granule Dosing Scheme

Selumetinib dose (mg) bid starting dose [a, b] without CYP3A4 and CYP2C19 inhibitors	Recommended granule dosage of selumetinib (mg) for co-administration with strong or moderate CYP3A4 and CYP2C19 inhibitors (20% reduction) [c]		Selumetinib granule dosage (mg) reduction for co-administration with strong or moderate CYP3A4 and CYP2C19 inhibitors[d]	
	AM	PM	AM	PM
CCI				

a. Actual dose in mg administered every 12 hours to achieve exposure approximately CCI to capsule in SPRINT; target median AUC = CCI ng/mL at selumetinib dose CCI mg/m^2 BSA.
b. Sprinkle capsule dose strengths are CCI and CCI mg, it is recommended that a single sprinkle capsule strength is used to achieve a dose level where possible, to avoid dosing error.
c. If the current dosage is up to CCI mg/m^2 bid, reduce to CCI mg/m^2 bid.
d. If the current dosage is up to CCI mg/m^2 bid, reduce to CCI mg/m^2 bid.

AUC, area under the concentration time curve; bid, twice daily; BSA, body surface area; CYP, cytochrome P450.

Table I24 Recommended Capsule Dosage of Selumetinib for Co-administration with Strong or Moderate CYP3A4 and CYP2C19 Inhibitors

BSA (m^2)	Recommended capsule dosage of selumetinib (mg) for co-administration with strong or moderate CYP3A4 and CYP2C19 inhibitors (20% reduction) [a]		Selumetinib capsule dosage (mg) reduction for co-administration with strong or moderate CYP3A4 and CYP2C19 inhibitors [b]	
	AM	PM	AM	PM
1.10 – 1.29	25	25	25	10
1.30 – 1.49	30	25	25	20
1.50 – 1.69	35	30	25	25
1.70 – 1.89	35	35	30	25
≥ 1.90	40	40	30	30

a. If the current dosage is up to 25 mg/m^2 bid, reduce to 20 mg/m^2 bid.
b. If the current dosage is up to 20 mg/m^2 bid, reduce to 15 mg/m^2 bid.

bid, twice daily; BSA, body surface area

Changes to, or addition of medications detailed in Table I25 and Table I26 should be avoided, unless clinically indicated. The lists in Table I25 and Table I26 are not intended to be exhaustive, and a similar restriction will apply to other agents that are known to affect CYP2C19, or CYP3A4 activity. Appropriate medical judgment is required. Please contact AstraZeneca with any queries.

Table I25 Inhibitors of CYP2C19 or CYP3A4 that AstraZeneca Recommends not to be Combined with Selumetinib

CYP2C19	CYP3A4
Strong	**Strong**
Fluconazole	Indinavir
Fluvoxamine	Nelfinavir
Fluoxetine	Ritonavir
Ticlopidine	Saquinavir
Moderate	Cobicistat
(S)-omeprazole (esomeprazole) high dose 80 mg BD [a]	Telapravir
Stiripentol	Itraconazole
Voriconazole	Ketoconazole
Triclabendazole	Voriconazole
Cannabidiol [b]	Troleandomycin
Fedratinib	Mifepristone
Omeprazole	Clarithromycin
Efavirenz	Lonafarnib
Moclobemide	Posaconazole
	Grapefruit juice
	Conivaptan
	Tucatinib
	Ceritinib
	Nelfinavir
	Ribociclib
	Idelalisib
	Moderate
	Erythromycin
	Fluconazole
	Atazanavir
	Duvelisib
	Diltiazem

CYP2C19	CYP3A4
	Dronedarone
	Crizotinib
	Fedratinib
	Letermovir
	Aprepitant
	Lefamulin
	Imatinib
	Verapamil
	Netupitant
	Nilotinib
	Tofisopam
	Berotralstat
	Ciprofloxacin
	Voxelotor
	Isavuconazole
	Cimetidine

a. There is literature evidence for esomeprazole causing weak CYP2C19 inhibition at 20 mg QD and moderate CYP2C19 inhibition at 80 mg QD, between this (eg, 20 mg BD) it is not confirmed at what dose esomeprazole changes from a weak to moderate inhibitor, therefore dose levels > 20 mg QD should be avoided with selumetinib.

b. There is literature evidence for cannabidiol causing moderate CYP2C19 inhibition at doses of 750 mg bid for 7 days. There are no data at what dose cannabidiol becomes a moderate inhibitor, or if lower doses of cannabidiol cause CYP2C19 inhibition.

BD, twice daily; CYP, cytochrome P450; QD, once daily.

Table I26 Inducers of CYP3A4 that AstraZeneca Recommends not to be Combined with Selumetinib

CYP3A4 Strong	CYP3A4 Moderate
Rifampin	Efavirenz
Mitotane	Dabrafenib
Rifapentine	Cenobamate
Apalutamide	Bosentan
Phenytoin	Rifabutin
Carbamazepine	Lorlatinib
Enzalutamide	Nafcillin
Ivosidenib	Phenobarbital
St John's wort	Modafinil
Lumacaftor	Pexidartinib

CYP3A4 Strong	CYP3A4 Moderate
	Etravirine
	Elagolix
	Sotorasib
	Telotristat ethyl
	Nevirapine

CYP, cytochrome P450.

Appendix J Clinical Outcome Assessments

J 1 CCI

Patient-reported outcomes questionnaire removed due to copyrights

J 2 CCI

Patient-reported outcomes questionnaire removed due to copyrights

J 3 CCI

CCI

J 4 CCI

CCI

J 5 CCI [redacted]

Patient-reported outcomes questionnaire removed due to copyrights

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J 6 Palatability Scale

Study Medication Palatability Assessment

Observer Assessment for Children

Instructions to carers/parents – Immediately after administration of the selumetinib granule formulation, capture the child's assessment of the taste of the medication.

1 Did your child take their study medication this [morning/evening]?
   - o Yes (go to Question 3)
   - o No (go to Question 2)

2 What was the reason for missing the dose?
   (a) Study doctor/nurse told me to skip the dose (no further questions to be answered).
   (b) I forgot to give my child the dose (no further questions to be answered).
   (c) My child did not want to take the dose (go straight to question 4).
   (d) My child could not swallow the study medication (go straight to question 4).
   (e) Other (go straight to question 3).

3 Choose the response that best matches a description of what you observe of the child's willingness to swallow the study medication.
   – Willingness to Swallow
      - o Swallowed without problem
      - o Some resistance but did swallow
      - o Spit out some/all of medication
      - o Vomited up medication

4 Was any behaviour observed when the study medication was given to this child that would be indicative of a negative response to the palatability of the study medication? *Palatability is the overall acceptance of the selumetinib granule medicine taken using soft food (as per the Handling Instructions) including taste, flavour, smell, amount of soft food used to take the medicine and texture.*
   - o Yes
   - o No

If answered Yes, please answer the following questions:

   (a) Did the child turn their head to reject intake of the medication?
      - o Yes
      - o No

(b) Did the child twist their face or mouth in an expression of displeasure?
- o Yes
- o No

(c) Did the child display any other negative behaviour?
- o Yes
- o No

Handling and Dosing

1 Were you able to prepare and dose the granules according to the Handling Instructions?
- Yes
- No (go to Question 2)

2 If no, please indicate which area/s you had difficulty in following?
(a) Difficulty identifying a suitable soft food.
(b) Identifying which sprinkle capsules are required for the dose.
(c) Opening of sprinkle capsule.
(d) Pouring the granules onto a spoon.
(e) Pouring the granules into a dosing cup.
(f) Adding soft food to the granules.
(g) Mixing the soft food with the granules.
(h) Giving the granules from a spoon.
(i) Giving the granules from a dosing cup.
(j) When using a dosing cup, adding further soft food to ensure the whole dose was taken.
(k) Giving the whole dose within 30 minutes.
(l) Other.

Appendix K 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 participant's safety. If in doubt, please contact the AstraZeneca Medical Monitor.

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 8. 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.

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 Astra Zeneca Medical Monitor.

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 study intervention. If this delay is outside the screening window specified in Section 5.4 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant. The procedures detailed in Table 2 must be undertaken to confirm eligibility using the same randomisation number as for the participant.

Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service may visit the participants home/or other remote location as per local Standard Operating Procedures, applicable.

Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP.

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 AEs and concomitant medication to be reported and documented.

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 the source documents, or by the participant themselves.

Home Delivery of Study Drug 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 minimise interruption of selumetinib administration during other study disruptions, eg, site closures due to natural disaster.

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 (i.e., 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 Astra-Zeneca-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 L Abbreviations

Abbreviation or special term	Explanation
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-6	Area under the concentration-time curve from time zero to 6 hours
AUC0-12	Area under the concentration-time curve from time zero to 12 hours
AUC0-24	Area under the concentration-time curve from time zero to 24 hours
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration
B	Blood
CCI	CCI
bid	Twice daily
BNP	Brain natriuretic protein
BP	Blood pressure
BSA	Body surface area
C	Cycle
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CK-MB	Creatine kinase-myocardial band
CK-MM	Creatine kinase-muscle
CLss/F	Apparent total clearance of the drug from plasma at steady state
CL/F	Apparent total clearance of the drug from plasma
Cmax	Maximum peak plasma concentration
COA	Clinical Outcome Assessment
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CR	Complete response
CRO	Contract research organisation
CSP	Clinical study protocol

Abbreviation or special term	Explanation
CSR	Central serous retinopathy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trials Information System
CV	Coefficient of variation
CYP	Cytochrome P450
D	Day
CCI	CCI
DES	Data entry site
DCO	Data cut-off
DILI	Drug-induced liver injury
CCI	CCI
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEA	European Economic Area
EoT	End of Treatment
ePRO	Electronic patient-reported outcomes
ERK	Extracellular signal-regulated kinase
EU	European Union
FDA	Food and Drug Administration
CCI	CCI
CCI	CCI
FU	Follow-up
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
CCI	CCI
CCI	CCI
GTPase	Guanosine 5'-triphosphatase
Hb	Haemoglobin
HCP	Health Care Professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HL	Hy's Law

Abbreviation or special term	Explanation
HLT	High level term
CCI	CCI
IATA	International airline transportation association
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICR	Independent central review
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IMP	Investigational medicinal product
IND	Investigational New Drug
INR	International normalised ratio
International co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator coordinating the Investigators and/or activities internationally.
IOP	Intraocular pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
KM	Kaplan-Meier
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities;
MEK	Mitogen activated protein kinase
MEKi	Mitogen activated protein kinase inhibitor
Min	Minimum
MPNST	Malignant peripheral nerve sheath tumours
MRI	Magnetic resonance imaging
n	Number
NC	Not calculated
NCA	Non-compartmental analysis
NCI	National Cancer Institute
NEC	Not elsewhere classified

Abbreviation or special term	Explanation
NF1	Neurofibromatosis type 1
NIH	National Institutes of Health
NIMP	Non-investigational medicinal product
OAT3	Organic ion transporter 3
ORR	Objective response rate
P	Plasma
P-A	Posterior-anterior
PBMC	Peripheral blood mononuclear cells
PBPK	Physiologically based pharmacokinetics
PD	Progressive disease
CCI	CCI
pERK	Phosphorylated extracellular signal-regulated kinase
CCI	CCI
PHL	Potential Hy's Law
PK	Pharmacokinetic(s)
PN	Plexiform neurofibroma
POB	Pediatric Oncology Branch
PR	Partial response
PRO	Patient-Reported Outcomes
PT	Preferred term
QTcB	QT interval corrected by Bazett's method
QTcF	QT interval corrected by Fridericia's method
Rac	Relative accumulation ratio
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
RNA	Ribonucleic acid
RPED	Retinal Pigment Endothelial Detachment
RT-PCR	Reverse transcription polymerase chain reaction
RTSM	Randomisation and Trial Supply Management
RVO	Retinal vein occlusion
S	Serum
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SMQ	Standardised MedDRA query

Abbreviation or special term	Explanation
SoA	Schedule of Activities
SoC	Standard of care
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
TBL	Total bilirubin
t½λz	Elimination half life
tlast	Time to last measurable concentration
tmax	Time to maximum concentration
TPV	Third Party Vendor
CCI	CCI
CCI	CCI
U	Urine
ULN	Upper limit of normal
US	United States
V	Visit
VMI	Visual-Motor Integration
VO_2	Maximal oxygen uptake
Vss/F	Apparent volume of distribution at steady state after non-intravenous administration
Vz/F	Apparent volume of distribution after non-intravenous administration
W	Week
WBC	White blood cell

Appendix M Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 3.0 (14 February 2023)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13) as it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The main purpose of the amendment is to clarify the requirement that the SRC will evaluate data during the dose finding phase after the first cycle of dosing: i) in '3 (maximum 4) evaluable participants' instead of 'the first 3 evaluable participants', and ii) that if a patient is classed as non-evaluable, additional patients will be dosed to ensure there is a minimum of 3 evaluable participants. Clarifications have been made and other typographical errors have been corrected.

Summary of Non-substantial Changes

Section Number and Name	Description of Change	Brief Rationale
Overall Design, 6.1.2.2 Definition of an Evaluable Participant for the Dose finding Phase , 9.2 Sample Size Determination	Change to definition of evaluable patient (for both sample size and SRC)	Clarification to existing CSP language
Section 1.3, Schedule of Activities (Table 2)	Foot note z added “Consent can be performed from Day -42. All screening assessments must be performed within 28 days prior to dosing.”	To provide flexibility for consenting process
Figure 2 Dose finding phase	Updated flow diagram with “3 evaluable participants…” instead of ‘Recruit 3 participants’ & “continue dosing into cohort…” instead of ‘continue recruitment into cohort…’	To align with the amended wording in Section 6.1.2 (Dose finding phase of the CSP.
Overall design , Section 4.1.2 Overall design	Corrected text from 3 participants to dosing in 3 evaluable participants in Cohort 1	To align with the requirement in section 6.1.2 (Dose finding phase) of the CSP that data from 3 evaluable participants is required

Section Number and Name	Description of Change	Brief Rationale
Section 5.4 Screen Failure	Clarification provided and text revised	To align with amended wording
Section 6.1.2 Dose Finding Process	Clarification provided to indicate that SRC will occur after 3 evaluable participants (maximum 4) instead of 3 evaluable participants. Clarification that if a patient is classed as non-evaluable, additional participants will be dosed to ensure there is a minimum of 3 evaluable participants. Clarified that whilst the SRC convenes 'dosing' of additional participants will be paused instead of 'recruitment'.	To clarify that data from 3 evaluable patients is needed for the SRC review, and that data from a maximum of 4 evaluable participants may be available
Section 6.3 Measures to Minimise Bias: Randomisation and Blinding	Text added "Informed consent may be signed within 42 days of dosing window if it is more convenient for the site and families ."	To align with the amended wording in Section 1.3, Schedule of Activities (Table 2)
Table 7 Initial Proposed Granule Formulation Dose Schema for Selumetinib	Rectified typo error for Dose level	Clarification
Appendix H , Table H25 Inhibitors of CYP2C19 or CYP3A4 that AstraZeneca Recommends not to be Combined with Selumetinib	Typo corrected to mention footnote "b" for Cannabidiol	Clarification

Amendment 2.0 (Version 3.0): (30 November 2022)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13) as it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:

The main purpose of the amendment is to include a new exploratory endpoint for biomarker analysis of residual PK or PD samples. The synopsis has been updated in line with changes to the protocol. Clarifications have been made and other typographical errors have been

corrected.

Summary of Non-substantial Changes

Section Number and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Inclusion of new exploratory objective.	To enable biomarker analysis of residual PK or PD samples
Section 1.1 Synopsis, Section 4.1.2 Overall Design, Section 6.7 Continued Access to Study Intervention after the End of the Study	Additional text added for post-trial access to selumetinib.	Update of AstraZeneca standard text
Section 1.3 Schedule of Activities, Table 2, footnote c	Text revised to clarify that an EoT visit will be performed for participants who permanently discontinue study intervention instead of selumetinib treatment.	Clarification
Section 1.3 Schedule of Activities, Table 2, footnote v	Removal of text 'for an individual at least 5 samples during 8-hour time period post first dose'.	Clarification
Section 4.4 End of Study Definition	New AstraZeneca standard text has been added to define the end of study as per EU and FDA regulatory requirements. The definition of study completion for individual participants has been added.	To provide guidance
Section 5.2 Exclusion Criteria (criterion 9)	Clarified that participants with known glaucoma that is clinically pain-free, has no clinically meaningful vision and has increased IOP may be permitted. Participants with any other significant abnormality on ophthalmic examination should be reviewed for potential eligibility.	Clarification based on UK health authority feedback
Section 5.3.1 Meals and Dietary Restrictions	Update of list for fruit and juices to avoid.	Added information to AstraZeneca standard text
Section 6.1.2.1 Pharmacokinetics and Safety/Tolerability Acceptability Criteria for the Dose finding Phase	Clarification on how the dose schema will be adjusted, and when it will not need to be adjusted.	An exposure change (as measured by AUC0-12) less than 30% will not impact the safety or efficacy of selumetinib in paediatric participants

Section Number and Name	Description of Change	Brief Rationale
Section 6.1.2.2 Definition of an Evaluable Participant for the Dose-finding Phase	New text added to clarify the definition of an evaluable participant for safety in the dose-finding phase.	To avoid confusion with regards to the definition of an evaluable participant for the dose-finding phase
Section 8.4.11 Medication Error, Drug Abuse, and Drug Misuse	New subsections added to provide additional information on medication error, drug abuse, and drug misuse.	Update of AstraZeneca standard text
Section 8.6 Human Biological Samples	The maximum storage time of biological samples has been updated to a maximum of 15 years from the date of the issue of the clinical study report in line with consent and local requirements.	Updated information
Section 8.7.1 Collection of Mandatory Samples for Biomarker Analysis	Text amended to clarify there is no additional biomarker sample collection in this study.	To enable biomarker analysis of residual PK or PD samples
Section 8.7.2 Other Study-related Biomarker research	New section of text included.	New information added to enable biomarker analysis of residual PK or PD samples
Section 9.4.5 Other Analyses	Inclusion of new text for biomarker exploratory analyses.	New information added to enable biomarker analysis of residual PK or PD samples
Appendix A 1 Regulatory and Ethical Considerations	Update of AstraZeneca standard text to include detail of guidance to be followed including the Declaration of Helsinki, 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.	Update of AstraZeneca standard text
Appendix A 1 Regulatory and Ethical Considerations	New subsection added on ‘Regulatory Reporting Requirements for Serious Breaches’.	Update of AstraZeneca standard text
Appendix A 7 Data Quality Assurance	Bullet point added to confirm that AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study.	Update of AstraZeneca standard text
Appendix B 4 Medication Error	A wrong dose (error greater than ± 10%) has been added as an example of drug not administered as indicated. New text on drug abuse and misuse has been added.	Update of AstraZeneca standard text

Section Number and Name	Description of Change	Brief Rationale
Appendix I Guidance Regarding Potential Interactions with Concomitant Medications	Footnote added to clarify that there is literature evidence for cannabidiol causing moderate CYP2C19 inhibition at doses of 750 mg bid for 7 days. There are no data at what dose cannabidiol becomes a moderate inhibitor, or if lower doses of cannabidiol cause CYP2C19 inhibition.	Clarification
Global	Minor editorial changes to wording and formatting.	To aid readability

AUC0-12, area under the concentration-time curve from time zero to 12 hours; CFR, Code of Federal Regulations; EoT, End of Treatment; EU, European Union; FDA, Food and Drug Administration; ICH, International Conference on Harmonisation; IEC, Independent Ethics Committee; IRB, Institutional Review Board; n, number: PK, pharmacokinetics.

Amendment 1.0 (Version 2.0): (18 March 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment

The main purpose of the amendment is to add a new cohort of participants in Japan in order to generate PK and safety data from Japanese patients enrolled in Japan, add a new CCI CCI exploratory endpoint, align to the updated IB, and to respond to Health Authority feedback. The synopsis has been updated in line with changes to the protocol. Clarifications have been made and other typographical errors have been corrected.

Changes are grouped according to whether they are Substantial or Non-Substantial.

Summary of Substantial Changes

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Section 1.2 Schema, Section 2.2 Background, Section 4.1.2 Overall Design, Section 0 Scientific Rationale for Study Design, Section 6.1.2 Dose-finding Phase, Section 9.2 Sample Size Determination, Section 9.3 Populations for Analyses, Section 9.4.1 General Considerations	Amended to include information relating to the addition of participants in Japan (Japan Cohort), including background information, number of planned participants in the cohort, clarification that PK data for the Japan Cohort will be summarised separately to the PK data for the Global Cohorts, clarification about the 3 analysis time points in relation to the Global and Japan Cohorts and clarification that the Japan Cohort will not be included in the dose-finding phase.	In order to generate PK and safety data from Japanese participants enrolled in Japan
Synopsis, Section 1.3 Schedule of Activities, Table 2, Section 6.1.1 Investigational Product, Section 8.6.1.1 Collection of Samples, Table 15	New column added to Table 2 to show what assessments are to be made on Day 7 after transition of participants to the capsule formulation. Addition of text to state that upon transition of participants from the granule formulation to the capsule formulation, PK sampling should be performed on Day 7 (range Day 4 to 14) and associated sampling timepoints.	Based on Health Authority feedback to include intensive PK sampling after transition of participants from granule to capsule formulation
Section 5.2 Exclusion Criteria, exclusion criterion 5, Section 8.3.4 Electrocardiograms	QTcB changed to QTcF. "Corrected QT" changed to QTcF and clarification added that if participants were enrolled using QTcB at screening (i.e., prior to this amendment) both QTcB and QTcF are to be collected at all timepoints throughout the study.	Based on Health Authority feedback

PK, pharmacokinetic; QTcB, QT interval corrected by Bazett's method; QTcF, QT interval corrected by Fridericia's method.

Summary of Non-substantial Changes

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Section 1.2 Schema, Section 4.1.2 Overall Design	Text amended to state that enrolment into the Global Cohorts will be stratified by age group; previously the protocol incorrectly implied that enrolment into the initial dose-finding phase was stratified by age group.	To correct an error

Section Number and Name	Description of Change	Brief Rationale
Synopsis, Section 2.1 Study Rationale	Text added to the rationale to make it clear that the relative bioavailability of selumetinib capsules to granules has already been investigated in adults therefore does not need to be repeated in paediatric participants.	For clarification
Synopsis, Section 2.1 Study Rationale, Section 9.4.2.1 Primary and Secondary Endpoints	Text added to clarify that at the final sample size for the recommended dose schema in the Global Cohorts the AUC0-12 geometric mean and CCI% CI will be determined for each age group and overall. Also clarified that exposure to selumetinib across the age groups in the SPRINKLE study will be considered comparable with exposure in the SPRINT study if the CCI% CI falls within CCI CCI% of the geometric mean AUC0-12 observed in SPRINT.	For clarification
Synopsis, Section 3 Objectives and Endpoints, Table 5, Section 8.6.1.1, Collection of Samples	A new exploratory objective to determine the PK of selumetinib and N-desmethyl selumetinib after administration of the selumetinib capsule formulation was added.	Based on Health Authority feedback
Synopsis, Section 3 Objectives and Endpoints, Table 5, Section 9.4.2.2 Secondary Endpoint(s)	PK parameters updated to align with AstraZeneca standards.	In order to align with previously reported data
Synopsis, Section 6.1.2.1 Pharmacokinetics and Safety/Tolerability Acceptability Criteria for the Dose finding Phase	In the primary PK analysis text, "CCI percentile" was changed to "CCI percentile". Geometric mean was changed to median as this was the parameter used to set these criteria.	To correct terminology
Synopsis, Schedule of Activities Table 2, Section 3 Objectives and Endpoints Table 5, Section 8.3.10.1 Neurodevelopment Tests	Amendment to clarify that the CCI CCI is derived from the CCI CCI, that both the CCI CCI will be performed, and that only the CCI test is required CCI CCI.	For clarification

Section Number and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, Table 2	Addition of dispensing and return of medication/compliance checks at Cycle 19. Addition of row to indicate daily drug diaries are to be completed twice daily from Cycle 1 Day 1 to Day 7 after transition to capsule formulation. Addition of dispense/return ePRO device/review ePROs check at Day 7 after transition to capsule formulation. Addition of review daily drug diary check at Day 7 after transition to capsule formulation.	For clarification
Section 1.3 Schedule of Activities, Table 2	The assessment of disease characteristics at screening (including documenting location of the target and non-target PN [if applicable], any PN-related symptoms and results of any previous genetic testing for NF1) was added.	To enable collection of data for any previous genetic testing for NF1
Section 1.3 Schedule of Activities, Table 2	The need for PN assessments using volumetric MRI at the end of treatment was replaced by instruction to follow standard of care.	To reduce the participant burden of multiple MRIs in a close period of time
Synopsis, Section 3 Objectives and Endpoints, Table 5, Section 9.4.2.2 Secondary Endpoint(s)	A new exploratory objective to complete pooled CCI and exposure-response analyses for safety, biomarkers, and efficacy was added. Information added regarding CCI CCI analyses; they will be described in the modelling analysis plan and reported separately from the main Clinical Study Report.	Based on Health Authority feedback
Section 5.2 Exclusion Criteria	"Bilirubin" amended to "Total bilirubin"	To correct an inconsistency
Section 6.5 Concomitant Therapy, Appendix I Guidance Regarding Potential Interactions with Concomitant Medications	Addition of text to state that selumetinib is an inhibitor of OAT3 and as such substrates of OAT3 should be given with caution.	To align to the updated IB, per EMA guidance
Section 8.6.1.2 Determination of Drug Concentration	Covance replaced by Labcorp as the assay laboratory	Update to assay laboratory
Appendix I Guidance Regarding Potential Interactions with Concomitant Medications	Updated Table I25 and Table I26 to include more concomitant medications.	To make the list of concomitant medications with potential interactions more comprehensive

EMA, European Medicines Agency; IB, Investigator's Brochure; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; OAT3, organic ion transporter 3; PD, pharmacodynamic; PK, pharmacokinetic; PN, plexiform neurofibroma.

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