| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | Selumetinib |
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# A Phase III, Multicentre, International Study with a Parallel, Randomised, Double-blind, Placebo-controlled, 2 Arm Design to Assess the Efficacy and Safety of Selumetinib in Adult Participants with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET).

**Sponsor Name: AstraZeneca AB**

Legal Registered Address: AstraZeneca AB, 151 85 Södertälje, Sweden

**Regulatory Agency Identifier Number(s):**
**IND 122851; EudraCT Number 2020-005607-39**

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: D134BC00001**

**Amendment Number:** 3

**Study Intervention:** Selumetinib

**Study Phase:** Phase III

**Short Title:** Efficacy and Safety of Selumetinib in Adults with NF1 who have Symptomatic, Inoperable PN (KOMET)

**Medical Monitor Name and Contact Information will be provided separately.**

**International co-ordinating investigator:**

PPD, National Cancer Institute, Bethesda, MD, USA

**National co-ordinating investigator:**

PPD, Hôpital Henri-Mondor, Paris, France

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 3.0 (Version 4.0): (XX month 2023)

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 the removal of the fasting restriction after end of Cycle 24, change to 1st key secondary endpoint estimand and include an additional key secondary endpoint.

## Summary of Changes

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, Section 3, Section 9.4.2.1 | Include intercurrent event strategy for primary estimand | In line with ICH E9 (R1) addendum |
| Section 1.1, Section 3, Section 9.4.2.2.1 | Update 1st key secondary estimand | To address regulatory feedback |
| Section 1.1, Section 3, Section 9.4.2.2.2 | Upgrade secondary estimand PlexiQOL to an additional key secondary estimand of PlexiQOL | Update to company position that PlexiQOL intended for labelling purposes |
| Section 9.1, Section 9.5 | Modify MTP to include 2nd key secondary estimand PlexiQOL and further information (scenarios) about the testing of key secondary endpoints | Update to company position that PlexiQOL intended for labelling purposes and to clarify the testing strategy within a key secondary endpoint. |
| Section 1.1, Section 3, Sections 9.4.2.3.7, 9.4.2.3.9, 9.4.2.3.10, 9.4.2.3.11, 9.4.2.3.13 | Add estimate at each scheduled visits other than overall estimate over randomised treatment period for the following secondary endpoints: chronic target PN pain palliation, pain medication use, PII-pNF pain interference total score, PROMIS Physical Function scores, PedsQL (NF1 module acute version 3.0 – adult report) skin sensations domain, EQ-5D-5L and EQ-VAS | To align with change to key secondary estimand to address regulatory feedback |
| Section 8.1.8 | Remove endpoints description | Not applicable to this section |
| Appendix A7 | Updated information about retention timelines of records and documents to 25 years after study archiving or as required by local regulations | Update required to comply with EU CTR and global company requirement |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, 1.3; Table 1: Schedule of Activities; Section 5.2.1 and 6.1.1 | Added the following wording to lift the fasting restriction from the end of C24: From the end of Cycle 24 (Cycle 25 Day 1) participants will not be required to continue to observe the fasting restriction, i.e participant can eat at any time point in relation to each medication intake (study intervention capsules). Refer to Section 5.2.1 for the definition of participant fed state. | To allow study drug to be administered in the fed state; modification follows an updated and more complete analysis of the food effect data for the program |
| Section 1.1 and Section 4.1 | Added detail about the food restriction lifting after C24 | To align with removal of fasting restriction after C24; modification follows an updated and more complete analysis of the food effect data for the program |
| Section 1.1 and Section 3 and section 9.3 (Table 12) | Added an exploratory objective re efficacy in fed state after C24 and related new analysis set | To align with removal of fasting restriction after C24; modification follows an updated and more complete analysis of the food effect data for the program |
| Section 8.1.1 and 8.1.8 | Added text to clarify that if a participant taking part in the study had a target PN resection and remained in the study, MRI scans and PAINS-pNF data will continue to be collected. | Clarification |
| Global | Minor editorial changes to wording and formatting | To aid readability |

bid, Twice daily; BSA, Body surface area; C1D1, Cycle 1 Day 1; CFR, Code of Federal Regulations; CTIS, Clinical Trials Information System; CYP, Cytochrome P450; EU, European Union; FDA, Food and Drug Administration; ICH, International Conference on Harmonisation; IEC, Independent Ethics Committee; IOP, Intraocular pressure; IRB, Institutional Review Board; IRT, Interactive Response Technology; NF1, Neurofibromatosis type 1; PN, Plexiform neurofibroma; PK, Pharmacokinetics; UK, United Kingdom.

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol Title:**

A Phase III, Multicentre, International Study with a Parallel, Randomised, Double-blind, Placebo-controlled, 2 Arm Design to Assess the Efficacy and Safety of Selumetinib in Adult Participants with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET).

**Short Title:**

Efficacy and Safety of Selumetinib in Adults with NF1 who have Symptomatic, Inoperable Plexiform Neurofibromas (KOMET).

**Rationale:**

Selumetinib has been shown to be effective in the treatment of paediatric patients with NF1 who have symptomatic, inoperable PN and is approved in the US for the treatment of paediatric patients aged ≥ 2 years of age. Plexiform neurofibromas, whilst typically present at birth, can continue to manifest through late adolescence and early adulthood (Williams et al 2009) and are often associated with significant clinical symptoms including pain and motor dysfunction (Gross et al 2018). As spontaneous PN shrinkage and spontaneous resolution of symptoms associated with PN has been shown to be extremely unlikely (Akshintala et al 2020, Gross et al 2018), adults with NF1-PN continue to have a significant unmet need. This study will aim to inform the benefit risk profile of selumetinib in adults with NF1 who have symptomatic, inoperable PN.

**Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| **Primary** | |
| To compare the effect of selumetinib relative to placebo by assessment of confirmed partial and complete response rate (ORR) by end of Cycle 16 using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN. | Objective response rate is defined as the proportion of participants 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 PR (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) by end of Cycle 16 as determined by ICR per REiNS criteria.<br>The analysis will include all randomised participants with measurable target PN at |

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| | baseline per ICR. Data obtained while on-treatment from first dose up until progression (if progression occurs prior to end of Cycle 16), or the last evaluable assessment up to and including end of Cycle 16 in the absence of progression, will be included in the assessment of ORR. The measure of interest is the difference in ORR. See statistical considerations section 9.4.2.1 for the complete intercurrent events strategy. |
| **Key Secondary** | |
| To compare the effect of selumetinib relative to placebo by assessment of change in chronic target PN pain intensity from baseline in participants with a PAINS-pNF chronic target PN pain score of $\geq 3$ at baseline. | Difference of the means in the change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib and placebo amongst participants with a PAINS-pNF chronic target PN pain intensity score $\geq 3$ at baseline, and at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score, regardless of changes to the participants' chronic PN pain medication (treatment policy strategy). See statistical considerations sections 9.4.2.2 for the complete intercurrent events strategy. |
| To compare the effect of selumetinib relative to placebo by assessment of change in HRQoL from baseline in participants with NF1 who have symptomatic, inoperable PN. | Difference in the change from baseline in PlexiQoL total score at Cycle 12 between selumetinib and placebo amongst participants with a PlexiQOL total score at baseline and at least one post-baseline total score. See statistical considerations section 9.4.2.2.2 for the complete intercurrent events strategy. |
| **Secondary** | |
| To demonstrate the effectiveness of selumetinib by assessment of confirmed partial and complete response rate (ORR) using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN. | This ORR analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR and who received at least one dose of selumetinib, ie, single arm assessment of ORR. Data obtained while on-treatment from first selumetinib dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. |

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To demonstrate the effectiveness of selumetinib by assessment of DoR in participants with NF1 who have symptomatic, inoperable PN. | The duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression by ICR per REiNS criteria or death due to any cause. The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to study intervention discontinuation. Duration of response will be derived using while on-treatment MRI volumetric assessments. |
| To demonstrate the effectiveness of selumetinib by assessment of PFS in participants with NF1 who have symptomatic, inoperable PN. | Progression free survival is defined as the time from the date of first selumetinib dose until date of progression by ICR per REiNS criteria or death (due to any cause). The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib. Progression free survival will be derived using while on-treatment MRI volumetric assessments. |
| To demonstrate the effectiveness of selumetinib by assessment of TTP in participants with NF1 who have symptomatic, inoperable PN. | Time to progression is defined as the time from the date of first selumetinib dose until date of documented objective disease progression by ICR per REiNS criteria. The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib. Time to progression will be derived using while on-treatment MRI volumetric assessments. |

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To demonstrate the effectiveness of selumetinib by assessment of TTR in participants with NF1 who have symptomatic, inoperable PN. | Time to response is defined as the time from date of first selumetinib dose until the date of first documented objective response (which is subsequently confirmed), by ICR per REiNS criteria. The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR and who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to selumetinib discontinuation. Data obtained from first dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of TTR. Time to response will be derived using while on-treatment MRI volumetric assessments. |
| To demonstrate the effect of selumetinib relative to placebo by assessment of percentage change from baseline in target PN volume in participants with NF1 who have symptomatic, inoperable PN. | Difference in best percentage change from baseline in target PN volume by ICR per REiNS criteria between selumetinib and placebo during the randomised period. The analysis will include all participants randomised to study intervention with measurable target PN at baseline per ICR. The best percentage change from baseline in target PN volume will be derived using while on-treatment MRI volumetric assessments during the randomised period. |
| To compare the effect of selumetinib relative to placebo by assessment of chronic target PN pain palliation and time to chronic target PN pain palliation in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline. | Chronic target PN pain palliation is defined as improvement of ≥ 2 in average cycle PAINS-pNF chronic target PN pain intensity score and no increase in chronic PN pain medication compared to baseline for that cycle. Pain palliation will be assessed in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline.<br>• Difference in proportion of participants with chronic target PN pain palliation between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period.<br>• Time to chronic target PN pain palliation is defined as the time from the first dose of study drug until the cycle of chronic target PN pain palliation. |

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To compare the effect of selumetinib relative to placebo by assessment of pain medication compared with baseline. | Difference in change from baseline in pain medication use (as reported using the eDiary) and as assessed by the investigator) between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by assessment of pain interference compared with baseline. | Difference in change from baseline in PII-pNF pain interference total score between selumetinib and placebo at at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by assessment of physical functioning compared with baseline. | Difference in change from baseline in PROMIS Physical Function scores between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by further assessment of HRQoL compared with baseline. | Difference in change from baseline in the Skin Sensations domain from the PedsQL (NF1 module acute Version 3.0 – adult report) between selumetinib and placebo a at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by assessment of health status compared with baseline. | Difference in change from baseline in EQ-5D-5L between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| | Difference in change from baseline in EQ-VAS between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To evaluate the effect of selumetinib by assessment of physical functioning compared with baseline. | Change from baseline in PROMIS Physical Function items. |
| To evaluate the effect of selumetinib by assessment of HRQoL compared with baseline. | Change from baseline in PlexiQoL. |
| | Change from baseline in the Skin Sensations domain from the PedsQL (NF1 module acute Version 3.0 – adult report). |

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To evaluate the effect of selumetinib by assessment of health status compared with baseline. | Change from baseline in EQ-5D-5L (standardised measure of health status). Five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Change from baseline in EQ-VAS. |
| To assess the PK of selumetinib. | • Plasma concentrations and PK parameters of selumetinib including, but not limited to:<br>° Cmax, AUC(0-6), AUC(0-8), AUClast, CL/F, Vss/F, tmax, tlast derived after multiple dose administration.<br>• Plasma concentrations and PK parameters of N desmethyl selumetinib including, but not limited to:<br>° Cmax, AUC(0-6), AUC(0-8), AUClast, tmax , tlast derived after multiple dose administration.<br>° MPAUC and MPCmax after multiple dose administration.<br>Population PK-pharmacodynamic analyses will be completed to investigate the selumetinib exposure-response relationship for safety and efficacy. The analyses will be reported separately from the Clinical Study Report. |

| **Safety** | |
|---|---|
| To assess the safety and tolerability of selumetinib alone and as compared to placebo in adult participants with NF1 who have symptomatic, inoperable PN. | Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, urinalysis, physical exam, ECG (as clinically indicated), ECHO/cardiac MRI and ophthalmologic assessment. The safety analysis will include all randomised participants who receive at least one dose of study intervention.<br>Assessments related to AEs cover:<br>• Occurrence/Frequency<br>• Relationship to IP as assessed by investigator<br>• CTC grade<br>• Seriousness<br>• Death<br>• AEs leading to discontinuation of IP<br>• Other action taken related to IP<br>• AEs of special interest<br>• Other significant AEs<br>Vital signs parameters include systolic and diastolic BP, and pulse rate, respiration rate, oxygen saturation, body temperature and body weight.<br>Assessments cover:<br>• Observed value<br>• Absolute change from baseline values over time<br>Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis.<br>Assessments cover:<br>• Observed value<br>• Absolute change from baseline values over time<br>Echocardiogram/cardiac MRI assessments include measurement of LVEF.<br>Assessments cover:<br>• Observed value<br>• Absolute change from baseline values over time<br>Ophthalmologic assessments include best corrected visual acuity, IOP, and slit-lamp fundoscopy.<br>Assessments cover:<br>• Observed value |
| **Exploratory** | |
| To evaluate PFS during the randomised period on selumetinib and placebo in participants with NF1 who have symptomatic, inoperable PN. | Progression free survival is defined as the time from the date of first dose until date of progression by ICR per REiNS criteria or death (due to any cause).<br>The analysis will include all randomised participants.<br>Progression free survival will be derived using while on-treatment MRI volumetric assessments. |

| | |
|---|---|
| To compare the effect of selumetinib relative to placebo by assessment of spike target PN pain intensity. | Difference in change from baseline in PAINS-pNF spike target PN pain intensity between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To explore potential biomarkers in residual biological samples, which may influence the progression of neurofibromatosis and inoperable plexiform neurofibromas (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 is 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 |
| **The following exploratory objectives will be assessed over the entire duration of the study in all participants** | |
| To evaluate effect of selumetinib by assessment of chronic target PN pain intensity compared to baseline. | Change from baseline in PAINS-pNF chronic target PN pain intensity score. |
| To evaluate effect of selumetinib by assessment of spike target PN pain intensity compared to baseline. | Change from baseline in PAINS-pNF spike target PN pain intensity score. |
| To evaluate effect of selumetinib by assessment of chronic target PN pain palliation in participants with a PAINS-pNF chronic target PN pain score of $\geq 3$ at baseline. | Chronic target PN pain palliation is defined as improvement of $\geq 2$ in average cycle PAINS-pNF chronic target PN pain intensity score and no increase in chronic PN pain medication compared to baseline for that cycle. Pain palliation will be assessed in post baseline cycles in participants with a PAINS-pNF chronic target PN pain score of $\geq 3$ at baseline. |
| To evaluate effect of selumetinib by assessment of pain interference compared to baseline. | Change from baseline in PII-pNF pain interference total score. |
| To evaluate effect of selumetinib by assessment of pain medication compared to baseline. | Change from baseline in pain medication:<br>• As reported using the e-Diary. |
| To evaluate the efficacy of selumetinib based on NF1 mutation alteration patterns | Differences in ORR, PN pain intensity in subgroups if feasible based on NF1 mutation alteration patterns |
| **Exploratory endpoints assessed after end of Cycle 24 in fed conditions** | |
| To evaluate efficacy under fed dosing of selumetinib | Percentage change from baseline in target PN volume at Cycle 30 and 36. |

AE, adverse event; AUC(0-6), area under the concentration-time curve from time 0 to 6 hours; AUC(0-8), area under the concentration-time curve from time 0 to 8 hours; AUClast, area under the concentration-time curve from time 0 to time of last quantifiable concentration; BP, blood pressure; CL/F, apparent total body clearance of the drug from plasma after extravascular administration; Cmax, maximum observed concentration; CR, complete response; CTC, Common Terminology Criteria; DoR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; EQ-5D-5L, EuroQol 5-Dimension 5-level; EQ-VAS, EuroQol visual analogue scale; HRQoL, health related quality of life; ICR, independent central review; IOP, intraocular pressure; IP, investigational product; LVEF, Left ventricular ejection fraction; MEK, Mitogen activated protein kinase; MPAUC, Metabolite: parent ratio based on AUC; MPCmax, Metabolite:parent ratio based on Cmax; MRI, magnetic resonance imaging; NF1, Neurofibromatosis type 1; ORR, Objective response rate; PAINS-pNF, PAin INtensity Scale for Plexiform Neurofibromas; PedsQL, Paediatric Quality of Life Inventory; PFS, Progression free survival; PII-pNF, Pain interference index – plexiform neurofibroma; PK, pharmacokinetic(s); PlexiQoL, Plexiform Neurofibroma Quality of Life scale; PN, Plexiform neurofibroma(s); PR, partial response; PROMIS, Patient-Reported Outcomes Measurement Information System; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; tlast, time of last observed concentration; RNA, Ribonucleic acid; tmax, time to reach maximum observed concentration following drug administration; TTP, time to progression; TTR, time to response; Vss/F, volume of distribution (apparent) at steady state after extravenous administration.

**Overall Design**

This is a Phase III, multicentre, international study with a parallel, randomised, double-blind, placebo-controlled, 2 arm design to assess the efficacy and safety of selumetinib in adult participants with NF1 who have symptomatic, inoperable PN.

During screening, a single target PN will be selected by the investigator and is defined as the clinically most relevant PN, which has to be measurable by volumetric MRI analysis (ie, a PN of at least 3 cm measured in one dimension, which can be seen on at least 3 imaging slices, and has a reasonably well-defined contour). If there is a second PN that is also considered clinically relevant and is measurable, the investigator may select this as a non-target PN; only one non-target PN can be selected.

As PN's are often associated with multiple co-morbidities such as pain and motor dysfunction, these elements will be assessed using various PRO tools.

Pain, associated with the target PN, will be assessed using the PAINS-pNF, a modified NRS-11 pain scale for use in NF1-PN that measures the participant's usual chronic tumour pain as well as sudden bursts of tumour pain that may occur, known as spikes of tumour pain. The average baseline chronic target PN pain intensity score will be used to stratify the participants into those who have a PAINS-pNF chronic target PN pain score of $\geq 3$ and those with milder, intermittent or no chronic pain, a PAINS-pNF chronic target pain score of $< 3$.

Chronic PN pain and spike pain medication use will be assessed during the study and all participants should have stable chronic PN pain medication use at baseline, defined as no clinically significant changes to prescribed chronic PN pain medication within 28 days prior to study enrolment or planned at the time of study enrolment. All participants will be expected to complete PN pain intensity assessments using the e-Diary in the screening period. During this

time, participants must complete their pain diary for at least 4 days out of 7 days for at least 2 weeks in order to determine the participant's average baseline chronic target PN pain intensity score which is required for stratification.

Participants will be randomised 1:1 to receive selumetinib or placebo; randomisation will be stratified by average baseline chronic target PN pain score and geographical region. Participants on the placebo arm will be crossed over to selumetinib treatment after the end of Cycle 12. Crossover to selumetinib treatment during the randomised period may be permitted at an earlier timepoint for participants with documented progression on imaging, as determined by ICR, per REiNS criteria. Participants will be blinded to their treatment during the randomised period. Following crossover to selumetinib treatment, subsequent treatment will be open-label.

The interim analysis (DCO1) will occur after the 100th randomised participant has had the opportunity to complete their end of Cycle 16 assessment and the primary analysis (DCO2) will occur after the last participant dosed (the last participant receiving first dose) has had the opportunity to complete their end of Cycle 16 assessment. The primary analysis of ORR will be assessed at the end of Cycle 16 landmark in all randomised participants with measurable target PN at baseline per ICR. The summary measure of the 1$^{st}$ key secondary endpoint is the difference in the mean change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib compared to placebo. This will be assessed in participants with a PAINS-pNF chronic target PN pain intensity score of $\geq 3$ at baseline and at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score. The summary measure of the 2$^{nd}$ key secondary endpoint is the difference in the mean change from baseline in PlexiQOL total score at Cycle 12 between selumetinib compared to placebo. This will be assessed in all randomized participants with a PlexiQOL total score at baseline and at least one post-baseline total score. The final analysis (Final DCO) will occur approximately 24 cycles post last participant dosed to further characterise selumetinib efficacy and safety. As each participant reaches the end of Cycle 24 (Cycle 25 Day 1), they will then be permitted to eat at any time point in relation to each selumetinib intake and considered in fed state. The data obtained in the fed state will be analysed in line with the main study analysis. Refer to Section 5.2.1 for the definition of participant fed state.

If the interim analysis DCO (DCO1) is due to take place within approximately 4 months of the primary analysis DCO (DCO2), then the interim analysis may not be performed and only the primary analysis will be performed.

**Disclosure Statement:**

This is a Phase III, parallel, randomised, double-blind, placebo-controlled, 2 arm multicentre, international study assessing the efficacy and safety of selumetinib compared with placebo in adult participants with NF1 who have symptomatic, inoperable PN.

**Participant Population:**

The target population of interest in this study is adult participants with NF1 who have symptomatic, inoperable PN where:

- Symptomatic is defined as clinically significant symptoms caused by the PN, as judged by the investigator; symptoms may include, but are not limited to, pain, motor dysfunction and disfigurement.
- Inoperable is defined as a PN that cannot be completely surgically removed without a risk of substantial morbidity (including significant bleeding or damage to nerves and/or surrounding vital structures) due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN; or unacceptable risk from the anaesthetic as assessed by the investigator.

**Number of Participants:**

It is estimated that approximately 212 participants with NF1 who have symptomatic, inoperable PN will be enrolled at approximately 46 sites across 13 countries to achieve approximately 145 participants randomised to study intervention. It should be noted that screening will continue until the required number of participants are randomised. If it is anticipated that 20% or more of participants (across blinded study intervention groups) withdraw prior to the end of Cycle 16, for reasons other than progression, then recruitment rates withstanding, enrolment will continue to randomise at least 50% of the total number of drop-out participants to ensure the primary endpoint is adequately powered.

**Note**: "Enrolled" means a participant's 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 are not randomly assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

**Intervention Groups and Duration:**

Following a screening period lasting up to 28 days, eligible participants will be randomised in a 1:1 ratio to one of the following intervention groups:

- Arm A: selumetinib 25 mg/m$^2$ orally bid
- Arm B: placebo orally bid

Randomisation will be stratified by average baseline PAINS-pNF chronic target PN pain score and geographical region. The number of participants randomised will be capped at approximately 106 participants with an average baseline PAINS-pNF chronic target PN pain score ≥ 3 and approximately 40 participants with an average baseline PAINS-pNF chronic target PN pain score < 3.

Participants in the selumetinib group will receive 25 mg/$m^2$ selumetinib as oral capsules bid until a selumetinib discontinuation criterion is met. Dosing will be based on BSA and capped at 50 mg bid when BSA is ≥ 1.9 $m^2$.

Participants in the placebo group will receive placebo as oral capsules twice daily and will be crossed over to selumetinib treatment after the end of Cycle 12.

The proposed duration for the study is approximately 24 months from last participant dosed to provide mature efficacy data as well as further safety and tolerability data. 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 and in the absence of discontinuation criteria.

**Follow-up of Participants Post Discontinuation of Study Intervention:**

After study intervention discontinuation, all participants will undergo an end-of-treatment visit and will be followed up for safety assessments 30 days after their last dose of study intervention (ie, the safety follow-up visit).

See Section 6.7 for a description of assessments following study DCO.

**Independent Data Monitoring Committee:**

Given that the randomised portion of the study is of limited duration, the participant population is not considered vulnerable and the safety profile of selumetinib is well established, an IDMC is not deemed to be necessary.

**Statistical Methods**

**Primary Estimand**

The primary endpoint of ORR by end of Cycle 16 includes all randomised participants with measurable target PN at baseline as determined by ICR (Measurable PN FAS). The ORR is defined as the proportion 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 PR (defined as a target PN volume decrease ≥ 20%, compared with baseline, confirmed by a consecutive scan within 3 to 6 months after the first response) by end of Cycle 16 as determined by ICR per REiNS criteria.

Intercurrent events are addressed as follows:

- Scans following randomised study intervention discontinuation will not be included in the analysis, assuming a while-on-treatment strategy to the intercurrent event of randomised study intervention discontinuation (including early crossover from placebo and progression) prior to end of cycle 16 due to any reason.

- Scans following the first 28 days of a prolonged study intervention interruption (defined as a study intervention interruption greater than or equal to 28 days) until study intervention has recommenced for at least 28 days will not be included in the analysis, assuming a while-on-treatment strategy to the intercurrent event of prolonged study intervention interruption.

- Scans after target PN surgical resection will be included in the analysis assuming a treatment policy approach to the intercurrent event of target PN resection.

- Scans after subsequent NF1-PN treatment will not be included in the analysis assuming a while-on-treatment strategy to the intercurrent event of subsequent NF1-PN treatment.

The primary endpoint ORR will be compared at the landmark end of Cycle 16 between selumetinib versus placebo using a Fisher's exact test. ORR in each treatment group will be presented with corresponding two-sided exact 95% confidence interval (CI) based on the Clopper-Pearson method (Clopper and Pearson 1934). The risk difference and 95% CI based on the Miettinen-Nurminen (score) method (Miettinen and Nurminen 1985) will also be presented.

**Key Secondary Estimands**

PAINS-pNF chronic target PN pain intensity

The 1st key secondary estimand is the difference of the means in the change from baseline in

PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib and placebo, amongst participants with a PAINS-pNF chronic target PN pain score ≥ 3 at baseline (Pain FAS) and at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score.

Intercurrent events are addressed as follows:

- Changes to participants' chronic PN pain medication will be included assuming the treatment policy strategy to the intercurrent event of changes in participant's chronic PN pain medication.

- PAINS-pNF scores following randomised study intervention discontinuation will not be collected and will be modelled through direct likelihood techniques assuming a hypothetical strategy to the intercurrent event of randomised study intervention discontinuation prior to end of cycle 12 due to any reason.

- PAINS-pNF scores after early crossover from placebo to selumetinib in participants with documented progression on imaging (as determined by ICR per REiNS criteria) will be set to missing assuming a while-on-treatment strategy to the intercurrent event of early crossover from placebo to selumetinib.

- PAINS-pNF scores after the first 28 days of a prolonged study intervention interruption until day prior to study intervention recommencement will be set to missing assuming a while-on-treatment strategy to the intercurrent event of prolonged study intervention interruption (defined as a study intervention interruption greater than or equal to 28 days).

- PAINS-pNF scores after a target PN surgical resection will be included in the analysis assuming a treatment policy approach to the intercurrent event of target PN resection.

The response variable for a cycle will be the average cycle PAINS-pNF chronic target PN pain score change from baseline defined as the average of the available daily PAINS-pNF chronic target PN pain scores for the 28 days up to and including the last day of the cycle minus the baseline chronic target PN pain score. The average cycle PAINS-pNF chronic target PN pain score will only be derived if the participant meets the criteria of having at least 4 daily pain scores out of 7 days for at least 3 nonoverlapping 7-day periods in the 28-day cycle. Baseline PAINS-pNF chronic target PN pain score is defined as the average of the available daily PAINS-pNF chronic target PN pain scores in the screening period (a minimum of 4 out of 7 days for at least 2 weeks).

The difference in the mean change from baseline in PAINS-pNF chronic target PN pain score at Cycle 12 between selumetinib and placebo and 95% CI will be assessed by means of a

mixed model for repeated measures (MMRM) with treatment, cycle number and geographic region as categorical fixed effects, the baseline PAINS-pNF chronic target PN pain intensity score as a continuous covariate and treatment-by-cycle number and baseline PAINS-pNF score-by-cycle number interactions. Parameters will be estimated with the restricted maximum likelihood (REML) approach and the Kenward-Roger approximation is used to estimate the degrees of freedom. An unstructured covariance matrix will be used to allow for unequal treatment variance and to model the correlation between different treatment measurements within the same subject. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, autoregressive and compound symmetry.

Missingness will be examined, and sensitivity analyses will be performed as appropriate. In addition, supplementary analyses for alternative estimands will be explored.

PlexiQOL

The 2nd key secondary estimand is the difference of the means in the change from baseline in PlexiQOL total score at Cycle 12 between selumetinib and placebo, amongst FAS participants with a PlexiQOL total score at baseline and at least one post-baseline total score.

Intercurrent events are addressed as follows:

- Post randomised study intervention discontinuation PlexiQOL scores will not be collected and will be modelled through direct likelihood techniques assuming a hypothetical strategy to the intercurrent event of randomised study intervention discontinuation prior to end of cycle 12 due to any reason.

- PlexiQOL scores after early crossover from placebo to selumetinib in participants with documented progression on imaging (as determined by ICR per REiNS criteria) will be set to missing assuming a while-on-treatment strategy to the intercurrent event of early crossover from placebo to selumetinib.

- PlexiQOL scores after the first 28 days of a prolonged study intervention interruption until day prior to study intervention recommencement will be set to missing assuming a while-on-treatment strategy to the intercurrent event of prolonged study intervention interruption.

- PlexiQOL scores after a target PN resection will be included in the analysis assuming a treatment policy approach to the intercurrent event of target PN resection.

The response variable for a specific cycle will be the PlexiQOL change from baseline, defined as the PlexiQOL total score at that cycle minus the baseline PlexiQOL total score.

The difference in the mean change from baseline at Cycle 12 will be analysed for PlexiQOL using a MMRM analysis. The MMRM model will include treatment, cycle number and geographical region as categorical fixed effects, the baseline PlexiQOL total score as a continuous covariate and treatment-by-cycle number and baseline PlexiQOL total score-by-cycle number interactions. Parameters will be estimated with the restricted maximum likelihood (REML) approach and the Kenward-Roger approximation is used to estimate the degrees of freedom. An unstructured covariance matrix will be used to allow for unequal treatment variance and to model the correlation between different treatment measurements within the same subject. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, autoregressive and compound symmetry.

Missingness will be examined, and sensitivity analyses will be performed as appropriate. In addition, supplementary analyses for alternative estimands will be explored.

**Sample Size**

With regard to the primary endpoint, a sample size of 73 participants per arm will have >99% power to detect the difference between selumetinib ORR of 20% and placebo ORR of 0%, considering a two-sided alpha of 5%.

Forty-two participants per arm are required for the study to have 90% power to detect a treatment difference of ≥ -2 in the 1st key secondary endpoint of the mean change from baseline of PAINS-pNF chronic target PN pain intensity score at Cycle 12 (assuming an SD of 2.8) in favour of selumetinib compared with placebo at a two-sided alpha level of 5%. To allow for approximately 20% drop out (ie, participants without at least one postbaseline average cycle PAINS-pNF chronic target PN pain score), 106 participants with baseline PAINS-pNF chronic target PN pain score ≥ 3 will be randomised in a 1:1 selumetinib:placebo allocation, ie, 53 participants per arm. In addition, approximately 40 participants with NF1 and a PAINS-pNF chronic target PN pain score of < 3 at baseline (including those with no PN pain) will be randomised 1:1 to receive selumetinib or placebo, ie, 20 participants per arm.

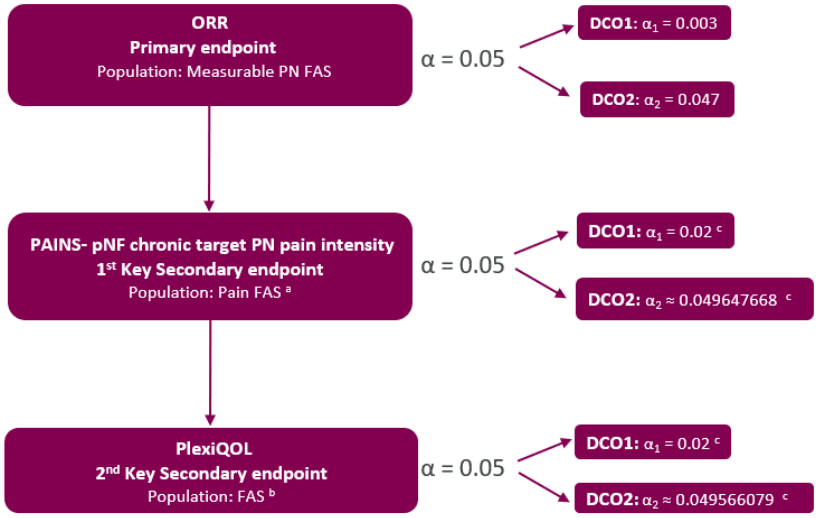
There is no formal sample size calculation regarding randomising 40 participants with baseline PAINS-pNF chronic target PN pain score of < 3; however, this is deemed sufficient to ensure the target population of adults with NF1 and symptomatic, inoperable PN (including those with little or no baseline PN pain) are represented.

**Multiplicity Testing Procedure**

To preserve the overall type 1 error (familywise error rate) at 5% (two-sided) in the strong sense, the MTP (described in Figure 1) including the primary endpoint (ORR by end of Cycle

16) and the key secondary endpoints (change from baseline in PAINS-pNF chronic target PN pain intensity at Cycle 12 and change from baseline in PlexiQOL total score at Cycle 12) will be implemented at the interim analysis (DCO1) and primary analysis (DCO2).

**Figure 1 Multiple Testing Procedure**




[a] Includes Pain FAS patients who have at least one post-baseline average cycle PAIN-pNF chronic target PN pain intensity score.

[b] Includes FAS patients who have a baseline PlexiQOL total score and at least one post-baseline PlexiQOL total score.

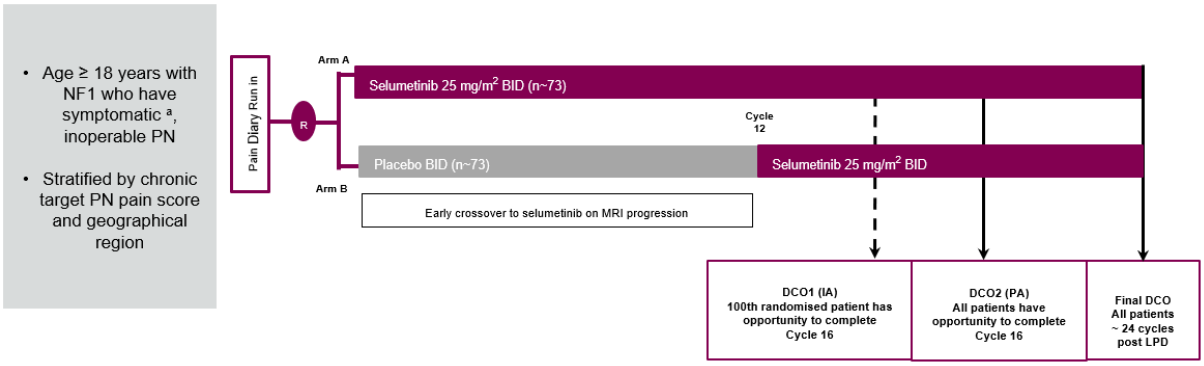
[c] Significance levels assuming 95.2% and 94.8% information fraction at DCO1 for 1st and 2nd key secondary endpoints, respectively. Final $\alpha_2$ will be determined at DCO1 based on the actual information fraction using the Haybittle-Peto procedure in EAST. With 100% information fraction at DCO1, $\alpha_1 = 0.05$.

DCO, data cut off; FAS, Full analysis set; $H_0$, null hypothesis; ORR, Objective response rate, PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PlexiQOL, Plexiform Neurofibromas Quality of Life; PN, plexiform neurofibromas.

Safety data will be summarised descriptively and will not be formally analysed unless otherwise specified.

## 1.2 Schema

**Figure 2 Study Design**




[a] Symptoms may include (but not limited to) pain, motor morbidity, disfigurement.
bid, twice daily; DCO, data cut-off; IA, interim analysis; LPD, last participant dosed; NF1, Neurofibromatosis type 1; PA, primary analysis; PN, Plexiform Neurofibroma; R Randomisation. From the end of Cycle 24 (Cycle 25 Day 1) participants will not be required to continue to observe the fasting restriction.

## 1.3 Schedule of Activities

The procedures for this study are presented in the SoA (Table 1 and Table 2).

## Table 1 Schedule of Activities

| | | | Intervention Period | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Screening[a]** | **Baseline pre-dose C1D1** | **C1 D8** | **C1 D28** | **C2 D28** | **C4 D28** | **C6 D28** | **C8 D28** | **C10 D28** | **C12 D28** | **C16 D28** | **C20 D28** | **C24 D28[W]** | **C30 [b] D28 onwards** | **EoT [c]** | **Safety Follow-up (30 days after last dose)** | **Ref in CSP** |
| **Study Day** | **Day – 28 to Day – 1** | **Day 1** | **Day 8** | **Day 28** | **Day 56** | **Day 112** | **Day 168** | **Day 224** | **Day 280** | **Day 336** | **Day 448** | **Day 560** | **Day 672** | | | | |
| **Window (days)** | | | Day 4-14 | **± 3** | **± 3** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **+ 7** | **+ 7** | |
| Informed consent: main study [d] | X | | | | | | | | | | | | | | | | A 3 |
| Informed consent genetic sample and analysis (optional) | X | | | | | | | | | | | | | | | | 8.7 |
| Inclusion and exclusion criteria | X | X | | | | | | | | | | | | | | | 5.1<br>5.2 |
| Randomisation [e] | | X | | | | | | | | | | | | | | | 6.3 |
| Demography | X | | | | | | | | | | | | | | | | 5.1 |
| Disease characteristics [f] | X | | | | | | | | | | | | | | | | 5.1 |
| Full physical examination [g] | X | X [h] | | | | | | | | | | | | | | | 8.2.1 |
| Targeted physical examination [g] | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | 8.2.1 |
| Height [i] | X | | | | | | | | | | | | | | | | 8.2.2 |

## Table 1 Schedule of Activities

| | | | Intervention Period | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Screening[a]** | **Baseline pre-dose C1D1** | **C1 D8** | **C1 D28** | **C2 D28** | **C4 D28** | **C6 D28** | **C8 D28** | **C10 D28** | **C12 D28** | **C16 D28** | **C20 D28** | **C24 D28[W]** | **C30 [b] D28 onwards** | **EoT [c]** | **Safety Follow-up (30 days after last dose)** | **Ref in CSP** |
| **Study Day** | **Day – 28 to Day – 1** | **Day 1** | **Day 8** | **Day 28** | **Day 56** | **Day 112** | **Day 168** | **Day 224** | **Day 280** | **Day 336** | **Day 448** | **Day 560** | **Day 672** | | | | |
| **Window (days)** | | | Day 4-14 | **± 3** | **± 3** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **+ 7** | **+ 7** | |
| Weight and BSA [i] | X | X [h] | | | | X | | X | | X | X | X | X | X | | X [l] | 8.2.2 |
| Medical history (past and current medical conditions) | X | X [h] | | | | | | | | | | | | | | | 5.1<br>5.2 |
| Clinical safety laboratory assessments (clinical chemistry, haematology, urinalysis) | X | X [h] | | X | X | X | X | X | X | X | X | X | X | X | X | X | 8.2.6 |
| Genomics initiative optional, exploratory genetic blood sample [j] | | X | | | | | | | | | | | | | | | 8.7 |
| 12-lead ECG [k] | X | X [h] | | | | | | | | | | | | | | X [l] | 8.2.4 |
| ECHO/cardiac MRI [l] | X | | | | | X | | X | | X | X | X | X | X | X [l] | X [l] | 8.2.5 |

## Table 1 Schedule of Activities

| | | | Intervention Period | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Screening[a]** | **Baseline pre-dose C1D1** | **C1 D8** | **C1 D28** | **C2 D28** | **C4 D28** | **C6 D28** | **C8 D28** | **C10 D28** | **C12 D28** | **C16 D28** | **C20 D28** | **C24 D28[W]** | **C30 [b] D28 onwards** | **EoT [c]** | **Safety Follow-up (30 days after last dose)** | **Ref in CSP** |
| **Study Day** | **Day – 28 to Day – 1** | **Day 1** | **Day 8** | **Day 28** | **Day 56** | **Day 112** | **Day 168** | **Day 224** | **Day 280** | **Day 336** | **Day 448** | **Day 560** | **Day 672** | | | | |
| **Window (days)** | | | Day 4-14 | **± 3** | **± 3** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **+ 7** | **+ 7** | |
| Ophthalmology examination [m] | X | | | | | | X | | | X | | | X | X [m] | X | X [m] | 8.2.7 |
| Performance status (ECOG) | X | X [h] | | | | X | | X | | X | X | X | X | X | X | | 8.2.8 |
| Pregnancy test [n] | X | X | Every cycle | | | | | | | | | | | | X | X | 8.2.6 |
| Vital signs [o] | X | X | | X | X | X | X | X | X | X | X | X | X | X | X | X | 8.2.3 |
| PN assessments using volumetric MRI [p] | X | | | | | X | | X | | X | X | X | X | X | X | | 8.1.1<br>8.1.2 |
| PAINS-pNF [q] | Daily e-Diary | | | | | | | | | | | | | | | | 8.1.8 |
| PN pain medication diary [q] | Daily e-Diary | | | | | | | | | | | | | | | | 8.1.8 |
| Drug Diary [r] | | | Daily e-Diary | | | | | | | | | | | | | | 6.4 |
| Investigator assessment of changes in pain medication [s] | | | | X | X | X | X | X | X | X | | | | | | | 8.1.8.3 |

## Table 1 Schedule of Activities

| | | | Intervention Period | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Screening[a]** | **Baseline pre-dose C1D1** | **C1 D8** | **C1 D28** | **C2 D28** | **C4 D28** | **C6 D28** | **C8 D28** | **C10 D28** | **C12 D28** | **C16 D28** | **C20 D28** | **C24 D28[W]** | **C30 [b] D28 onwards** | **EoT [c]** | **Safety Follow-up (30 days after last dose)** | **Ref in CSP** |
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| **Window (days)** | | | Day 4-14 | **± 3** | **± 3** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **+ 7** | **+ 7** | |
| PII-pNF | | X | | X | X | X | X | X | X | X | X | X | X | X | X | | 8.1.8 |
| PGIS | | X | | X | X | X | X | X | X | X | | | | | | | 8.1.8 |
| PGIC [t] | | | | X | X | X | X | X | X | X | | | | | X | | 8.1.8 |
| PROMIS physical function items | | X | | | X | X | | X | | X | X | X | X | X | X | | 8.1.8 |
| PedsQL (NF1 module acute Version 3.0 – adult report) Skin Sensations domain | | X | | | X | X | | X | | X | X | X | X | X | X | | 8.1.8 |
| EQ-5D-5L | | X | | | X | X | | X | | X | X | X | X | X | X | | 8.1.8 |
| PlexiQoL | | X | | | X | X | | X | | X | X | X | X | X | X | | 8.1.8 |
| Dispense study intervention | | X | | X | X | X | X | X | X | X | X | X | X | X | | | 6.1 |
| Return study intervention and compliance check | | | | X | X | X | X | X | X | X | X | X | X | X | X | | 6.4 |

## Table 1 Schedule of Activities

| | | | Intervention Period | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Screening[a]** | **Baseline pre-dose C1D1** | **C1 D8** | **C1 D28** | **C2 D28** | **C4 D28** | **C6 D28** | **C8 D28** | **C10 D28** | **C12 D28** | **C16 D28** | **C20 D28** | **C24 D28[W]** | **C30 [b] D28 onwards** | **EoT [c]** | **Safety Follow-up (30 days after last dose)** | **Ref in CSP** |
| **Study Day** | **Day – 28 to Day – 1** | **Day 1** | **Day 8** | **Day 28** | **Day 56** | **Day 112** | **Day 168** | **Day 224** | **Day 280** | **Day 336** | **Day 448** | **Day 560** | **Day 672** | | | | |
| **Window (days)** | | | Day 4-14 | **± 3** | **± 3** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** | **+ 7** | **+ 7** | |
| PK blood samples [u] | | | X | | | | | | | | | | | | | | 8.5.1 |
| AEs [v] | X | X | ←═══ | | | | | | | | | | | | | →| 8.3 |
| Concomitant medication/ procedures | X | X | ←═══ | | | | | | | | | | | | | →| 6.5 |

[a] The 28-day screening period will commence on the date the 'Screening Visit' transaction is registered in IRT system. Visit schedule should always be calculated in relation to C1D1. Visits should not be skipped or overwritten in IRT. If a visit (+ visit window) is missed, the visit should be completed as the earliest opportunity. If there is a long gap between the scheduled and actual visit, please check with global study team how visits are to be recorded.

[b] From Cycle 30 onwards, for all participants remaining on study intervention, assessments will be performed every 6 cycles with the exception of ophthalmic assessments (see footnote l) and pregnancy assessments (see footnote m).

[c] The 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 decision to discontinue treatment permanently has been made. If EoT is >30 days after last treatment dose, then the EoT assessments can also function as the 30-Day Safety follow-up visit.

[d] Screening tests should be performed within 28 days before the first administration of study intervention, unless otherwise indicated. Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[e] Every effort should be made to minimise the time between randomisation and starting treatment (maximum interval of 3 business days of randomisation).

[f] Assessment of baseline disease characteristics includes documenting location of the target and non-target PN (if applicable) and any PN-related symptoms and results of any previous genetic testing for NF1.

[g] The full physical examination includes an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic and neurological systems. Targeted physical examinations are to be used by the investigator on the basis of clinical observations and symptomatology. The targeted physical exam will include, at a minimum, assessments of the general appearance, respiratory and cardiovascular systems, skin and abdomen (liver and spleen).

[h] If screening assessments have been performed within 14 days prior to starting study intervention, they do not have to be repeated at Cycle 1 Day 1 if the participant's condition has not changed. A stable participant's condition since previous assessment should be documented in medical records.

[i] Height and weight measurements will be performed in light clothing and with shoes off. Body surface area should be calculated. Height, weight and BSA may be measured more frequently, if indicated. BSA should be calculated using Mosteller formula, see Section 8.2.2.

[j] The sample for genetic research will be obtained at Day 1 pre-dose. If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

[k] Performed at screening and baseline and then as clinically indicated. Participants should be semi-supine and at rest for at least 5 minutes prior to recording the ECG.

[l] The modality of the cardiac function assessments must be consistent for a given participant. The participant should be examined using the same machine and operator throughout the study wherever possible. Echocardiogram/cardiac MRI is not required at EoT visit if the participant has had an echo/cardiac MRI within 4 weeks prior to study intervention discontinuation, unless clinically indicated. Echocardiogram/cardiac MRI is only required at 30 day safety follow-up in participants who have abnormal findings at the time of selumetinib discontinuation/ EoT visit. 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 or cardiac MRI, ECG, vital signs, and weight performed at the 30 day safety follow-up.

[m] Ophthalmologic assessments may be performed more often, if clinically indicated. After 12 cycles, ophthalmological assessment will be performed every 12 cycles. Only required at the Safety Follow-up visit if abnormal findings at EoT assessment.

[n] Pregnancy testing will be performed at screening, Cycle 1 Day 1, and every cycle throughout the entire exposure period, in women of childbearing potential only. A serum pregnancy test is required at screening, following that a urine or serum pregnancy test is acceptable. Where a pregnancy test is the only assessment for a cycle, a clinic visit is not required as the test may be performed offsite. The site should obtain the test result from the participant prior to the next onsite visit.

[o] Temperature (same method to be used throughout the study), pulse rate, oxygen saturation by pulse oximetry, respiratory rate, and BP will be assessed. Assessments of BP and pulse rate should be assessed in a sitting position and preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Manual techniques will be used only if automated devices are not available. The average of 3 BP readings, taken consecutively at intervals of at least one minute apart will be recorded on the eCRF.

[p] The PN assessments will be performed at screening and every 4 cycles (16 ± 1 weeks) up to Cycle 24 (ie, at Cycle 4, 8, 12, 16, 20, and 24). After 24 cycles, PN assessments will be performed every 6 cycles (24 ± 1 weeks) as long as the participant remains on study intervention. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, the subsequent assessments at the next scheduled visit must be performed. All volumetric MRI scans should be performed relative to Cycle 1 Day 1, ie the time course should not change if the participant experiences a dose interruption or there are delays in previous scan visits.

[q] PAINS-pNF scores and PN pain medication should be collected on the daily e-Diary during screening, the intervention period and up to EoT. Chronic target PN pain intensity PAINS-pNF scores must be recorded for at least 4 days out of 7 days for at least 2 weeks during the screening period for a participant to be considered eligible for study.

[r] Participants will complete a daily drug diary during the interventional period to record whether study intervention was taken as instructed.

[s] The investigator will record in the eCRF if the participant's analgesic requirement has changed compared to baseline since it was last assessed. Assessments will be performed at site visits with additional telephone assessments at Cycle 3, Day 28; Cycle 5, Day 28; Cycle 7, Day 28; Cycle 9 Day 28 and Cycle 11 Day 28 (see Table 2).

[t] PGIC 1 'since your last visit to the study site' should be assessed at site visits Cycle 1, Day 28; Cycles 2, 4, 6, 8, 10, 12; PGIC 2 'since starting the study medication' should be assessed at Cycle 12 or EoT if the participant discontinues pre-Cycle 12.

[u] Blood samples to measure selumetinib and N-desmethyl selumetinib metabolite will be collected on Cycle 1 Day 8: Pre-Dose, 0.5 h, 1.5 h, 3 h, 6 h and 8 h post-dose. For operational reasons the PK sampling can take place on any day between Day 4 and Day 14 as long as the participant has received 3 consecutive days of dosing immediately prior to the PK day. Every effort should be made to conduct PK sampling within the Day 4 to Day 14 window. However, if for unforeseen reasons this is not possible, PK sampling can be performed ideally within the first cycle but no later than Cycle 12, provided the participant has received 3 consecutive days of dosing immediately prior to the PK day. The selumetinib dose dates and times must be recorded accurately on the day preceding the PK sample day and on the PK sample day.

[v] Adverse events will be collected from the time of signing the ICF, throughout the treatment period, and including the follow-up period. Adverse events will also be collected at additional telephone assessments on Cycle 3, Day 28; Cycle 5, Day 28; and Cycle 7, Day 28; Cycle 9 Day 28 and Cycle 11 Day 28, as per Table 2.

[w] From the end of Cycle 24 (Cycle 25 Day 1) participants will not be required to continue to observe the fasting restriction, i.e participant can eat at any time point in relation to each selumetinib intake.

Each treatment cycle is 28 days. Assessments will be performed at the end of each cycle. Study intervention will be dispensed after all assessments have been performed and evaluated by the investigator. Participant's second dose on the day of their on-site visit can be taken from newly dispensed study intervention. Treatment will not be held while end of cycle evaluations are ongoing. Note: Data collection following study analysis until the end of the study is described in Section 8.

AE, adverse event; BSA, body surface area; BP, blood pressure; CSP, clinical study protocol; C, cycle; D, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EoT, end of treatment; EQ 5D 5L, EuroQol 5-Dimension 5-level; ICF, informed consent form; IRT, Interactive Response Technology; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; PAINS-pNF, PAin INtensity Scale for Plexiform Neurofibromas; PedsQL, Paediatric Quality of Life Inventory; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PII-pNF, Pain Interference Index- Plexiform Neurofibroma; PK, pharmacokinetic(s); PlexiQoL, Plexiform Neurofibromas Quality of Life; PN, plexiform neurofibroma; PROMIS, Patient-Reported Outcomes Measurement Information System.

## Table 2 Schedule of Telephone Assessments

| | Intervention period | | | | |
|---|---|---|---|---|---|
| | **Cycle 3 Day 28** | **Cycle 5 Day 28** | **Cycle 7 Day 28** | **Cycle 9 Day 28** | **Cycle 11 Day 28** |
| Window (days) | **± 7** | **± 7** | **± 7** | **± 7** | **± 7** |
| Investigator assessment of changes in pain medication | X | X | X | X | X |
| Adverse events | X | X | X | X | X |
| Concomitant medication/ procedures | X | X | X | X | X |

# 2 INTRODUCTION

Selumetinib is an oral, potent, and highly selective allosteric MEK1/2 inhibitor with a short half-life that is being developed for the treatment of NF1-PN.

## 2.1 Study Rationale

Selumetinib has been shown to be effective in the treatment of paediatric patients with NF1 who have symptomatic, inoperable PN and is approved in the US for the treatment of paediatric patients aged ≥ 2 years of age. Plexiform neurofibromas, whilst typically present at birth, can continue to manifest through late adolescence and early adulthood (Williams et al 2009) and are often associated with significant clinical symptoms including pain and motor dysfunction (Gross et al 2018). As spontaneous PN shrinkage and spontaneous resolution of symptoms associated with PN has been shown to be extremely unlikely (Akshintala et al 2020, Gross et al 2018), adults with NF1-PN continue to have a significant unmet need. This study will aim to inform the benefit risk profile of selumetinib in adults with NF1 who have symptomatic, inoperable PN.

## 2.2 Background

Neurofibromatosis Type 1 is a rare, autosomal dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene (17q11.2), which encodes the tumour suppressor protein neurofibromin 1. Neurofibromin 1 is a GTPase-activating protein that promotes the conversion of active RAS GTP to inactive RAS guanosine 5'-diphosphate, thereby functioning as a negative regulator of the RAS proto-oncogene, which is a key signalling molecule in the control of cell growth (Gutmann et al 2012). Neurofibromin 1 mutation that leads to loss of function results in a failure to inactivate RAS.

Approximately half of NF1 cases are familial, with penetrance being 100%, and the remainder are the result of de novo (spontaneous) mutations (Evans et al 2010). Features of the disorder typically appear in early childhood and are fully penetrant by adulthood (Stewart et al 2018).

Neurofibromatosis Type 1 is characterised by progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and the associated clinical signs and symptoms can be severe. Affected individuals start life with one mutated (non-functional) 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 formation of tumours (including PN), by acquisition of a somatic NF1 mutation in selected cells (Gutmann et al 2013; Ruggieri and Packer 2001). Patients with NF1 have an increased risk of developing tumours of the central and peripheral nervous system.

Neurofibromas are benign Schwann cell tumours composed not only of neoplastic Schwann cells but also of non-neoplastic fibroblasts, mast cells, macrophages, endothelial cells, pericytes, and perineural cells. Plexiform neurofibromas are one of the most common benign tumours, occurring in approximately 20% to 50% of patients (Korf 1999; Mautner et al 2008).

Plexiform neurofibromas can have complex shapes and sometimes reach very large size with some documented as being 20% of body weight (Korf 1999; Mautner et al 2008). Plexiform neurofibromas may develop along nerves anywhere in the body.

Patients may have one or multiple PNs that result in clinical impact such as pain, neurological and motor dysfunction, airway compromise, visual impairment, or disfigurement. The severity may range from mild, with modest impact on daily activities, to severe. The symptoms or impact from the presence and growth of PNs are collectively termed PN associated symptoms (also referred to as morbidities in the literature and clinical community) and spontaneous resolution of these symptoms once developed has been shown to be extremely unlikely (Gross et al 2018).

Pain associated with PNs can interfere with daily activities despite analgesia (Wolters et al 2015). Heaney et al 2019 reported the impact of PNs on need fulfilment in adults. Patients reported restrictions on their independence due to the unpredictable nature of their PN symptoms. This results in greater dependence on family and friends, particularly as those with PN-related pain and discomfort found it difficult to devote attention to other issues. This also impacts on their need for role fulfilment as it leads to inability to work or take part in sports or hobbies. The NCI has conducted extensive qualitative research in order to understand the pain experience of adult patients with NF1 and PNs and to modify the standard NRS-11 to be more appropriate for this population. They found that patients with NF1-PN experience two types of PN-related tumour pain- chronic pain and spike pain:

- Chronic tumour pain (also known as usual tumour pain) is tumour pain that is present most of the time (described as “constantly there”, “it’s going to always hurt”, “pain is every single day”).
- Spikes of tumour pain (also known as episodic tumour pain) are sudden bursts of tumour pain that may occur spontaneously or in response to a stimulus (described as “a shock pain”, “like an electricity pain, it will come really fast, and then it leaves”, “if I hit against something”).

The tool developed by the NCI is known as PAINS-pNF and based on the above research has 2 items, one assessing participants’ experience of chronic PN-related pain intensity, and the other their experience of spikes of PN-related pain intensity, both for a target PN-location.

Selumetinib is a potent, selective, allosteric inhibitor of MEK that is non-competitive with respect to ATP, licensed for development by AstraZeneca Pharmaceuticals from Array BioPharma. Selumetinib is being co-developed by AstraZeneca and Merck & Co.

Selumetinib blocks MEK activity and inhibits growth of RAF-MEK-ERK pathway activated cell lines. Therefore, MEK inhibition can block the proliferation and survival of tumour cells in which the RAF-MEK-ERK pathway is activated. Neurofibromin-1 (encoded by the NF1 gene) is a negative regulator of RAS and therefore loss of function mutations in NF1 result in activation of the RAF-MEK-ERK pathway. In genetically modified mouse models of NF1 that generate neurofibromas that recapitulate the genotype and phenotype of human type 1 neurofibromas, oral dosing of selumetinib inhibits ERK phosphorylation, reduces neurofibroma volume, proliferation, number and growth. Selumetinib is being developed as a treatment for paediatric and adult patients with NF1 who have symptomatic PNs.

Selumetinib received approval in the US in April 2020 for the treatment of paediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN based on the Phase II Stratum 1 data of the SPRINT study (D1532C00057), coordinated by NCI POB under CTEP sponsorship and conducted in the US. Supportive efficacy data were provided by the Phase I data of the SPRINT study (Study 8799; NCI 11 C 0161, D1532C00057).

A detailed description of the chemistry, pharmacology, mechanism of action, 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 3. Guidance and algorithms for the management of these risks are described in Appendix H.

## Table 3 Risk Assessment

| Potential risk of clinical significance | Rationale for risk | Mitigation strategy |
|---|---|---|
| **Potential risks associated with selumetinib** | | |
| Gastrointestinal effects: diarrhoea, nausea, and vomiting | Frequently reported adverse reactions, typically low grade but may require management with dose interruptions and/ or reductions. | Manage with selumetinib dose interruptions and/ or reductions. See Appendix H for management guidelines for diarrhoea. |
| Retinal toxicity | Isolated cases of RPED, CSR, and RVO in adult patients with multiple tumour types, receiving treatment with selumetinib monotherapy and in combination with other anti-cancer agents, and in a single paediatric patient with pilocytic astrocytoma on selumetinib monotherapy, have been observed. | Exclusion of participants with: current or past history of RPED/CSR or RVO; IOP > 21 mmHg; or uncontrolled glaucoma (irrespective of IOP).<br>An ophthalmologic examination will be evaluated at the times outlined in the SoA, and as clinically indicated. See Appendix H for management guidelines. |
| Creatine phosphokinase increase | Elevations of CK are predominantly of low grade (1-or 2-grade increase from baseline) and are asymptomatic in the majority of patients. There were asymptomatic Grade 4 elevations in 2 paediatric patients. While there is no established relationship between selumetinib and myopathy, these events should be closely monitored. | Manage with selumetinib dose interruptions and/ or reductions. See Appendix H for management guidelines |
| Skin toxicity | Rash and dermatitis acneiform are very commonly reported in patients receiving selumetinib monotherapy, but maculopapular rashes have been also observed. Majority of the events are typically low grade and reversible, but may require management with dose modification. | No specific dermatological exclusion criteria are included in this study, however patients with persistent toxicities (CTCAE Grade ≥ 2) caused by previous therapy for NF1 PN, excluding hair changes such as alopecia or hair lightening will be excluded from participation. Dose interruptions and/or reductions. See Appendix H for management guidelines. |
| Left ventricular ejection fraction decreases | In both paediatric and adult populations taking selumetinib, reversible, asymptomatic reductions in LVEF have been recorded in a small number of patients. | Exclusion of participants with clinically significant cardiovascular disease or LVEF below LLN. Evaluate LVEF at regular intervals as per the SoA, or more frequently as clinically indicated, during treatment. See Appendix H for management guidelines. |

**Table 3 Risk Assessment**

| Potential risk of clinical significance | Rationale for risk | Mitigation strategy |
|---|---|---|
| Transaminase increases | Increases in serum ALT and AST levels have been observed in clinical studies with selumetinib. While the reported events have been typically low grade and no cases of Hy's law have been seen, elevated transaminase is a class effect and should be closely monitored to detect early liver toxicity. | Exclusion of participants with known moderate or severe hepatic impairment. Exclusion of participants with any evidence of severe uncontrolled systemic liver disease, including those with known hepatitis B, hepatitis C, or abnormal liver function test as transaminases > 2.5 × ULN and total bilirubin > 1.5 × ULN or > 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia). Liver function test monitoring will take place according to the SoA. |
| Increased BP | Increases in systolic BP and diastolic BP have been observed in clinical studies with selumetinib. Adverse events were generally CTCAE Grade 1 or 2 and asymptomatic, but some patients required amendment or initiation of antihypertensive medication. Study population has increased risk of NF1 vasculopathy, therefore these events should be closely monitored. | Patients with uncontrolled hypertension (at screening: BP ≥ 140/90 mmHg despite optimal therapy) would be excluded from the trial. Regular monitoring of vital signs is included in the SoA. |
| Increased exposure in Asian participants | Increased systemic exposure has been seen in adult Asian subjects, although there is considerable overlap with Western subjects when corrected for body weight. | No specific adjustment to the starting dose is recommended for Asian patients, however, these patients should be closely monitored for AEs. |

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CK, creatine kinase; CSR, central serous retinopathy; CTCAE, Common Terminology Criteria for Adverse Events; IOP, intraocular pressure; LLN, lower limit of normal; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; RPED, retinal pigment endothelial detachment; PN, plexiform neurofibroma; RVO, retinal vein occlusion; SoA, schedule of activities; ULN, upper limit of normal.

### 2.3.2 Benefit Assessment

Selumetinib has demonstrated compelling ORR, durability of response, improvement in clinical outcomes and symptoms, and quality of life along with a favourable tolerability profile in paediatric patients with NF1 who have symptomatic, inoperable PN. Furthermore, comparable efficacy has been observed in adults based on an ongoing Phase II paired-biopsy study (NCT02407405) in adult patients with NF1 and inoperable PN, sponsored by the NCI. The adult participants in the study may therefore benefit from treatment.

### 2.3.3 Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with selumetinib are justified by the anticipated benefits that may be afforded to participants with NF1 who have symptomatic, inoperable PN.

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

## 3 OBJECTIVES AND ENDPOINTS

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| **Primary** | |
| To compare the effect of selumetinib relative to placebo by assessment of confirmed partial and complete response rate (ORR) by end of Cycle 16 using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN. | Objective response rate is defined as the proportion of participants 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 PR (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) by end of Cycle 16 as determined by ICR per REiNS criteria.<br>The analysis will include all randomised participants with measurable target PN at baseline per ICR. Data obtained while on-treatment from first dose up until progression (if progression occurs prior to end of Cycle 16), or the last evaluable assessment up to and including end of Cycle 16 in the absence of progression, will be included in the assessment |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| | of ORR. The measure of interest is the difference in ORR. See statistical methods sections for the complete intercurrent events strategy. |
| **Key Secondary** | |
| To compare the effect of selumetinib relative to placebo by assessment of change in chronic target PN pain intensity from baseline in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline. | Difference of the means in the change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib and placebo amongst participants with a PAINS-pNF chronic target PN pain intensity score ≥ 3 at baseline, and at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score, regardless of changes to the participants' chronic PN pain medication (treatment policy strategy). See statistical methods sections for the complete intercurrent events strategy. |
| To compare the effect of selumetinib relative to placebo by assessment of change in HRQoL from baseline in participants with NF1 who have symptomatic, inoperable PN. | Difference in change from baseline in PlexiQoL total score between selumetinib and placebo at Cycle 12 amongst participants with a PlexiQOL total score at baseline and at least one post-baseline total score. See statistical considerations section 9.4.2.2.2 for the complete intercurrent events strategy. |
| **Secondary** | |
| To demonstrate the effectiveness of selumetinib by assessment of confirmed partial and complete response rate (ORR) using volumetric MRI analysis as determined by ICR (per REiNS criteria) in participants with NF1 who have symptomatic, inoperable PN. | This ORR analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR and who received at least one dose of selumetinib, ie, single arm assessment of ORR. Data obtained while on-treatment from first selumetinib dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To demonstrate the effectiveness of selumetinib by assessment of DoR in participants with NF1 who have symptomatic, inoperable PN. | The duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression by ICR per REiNS criteria or death due to any cause. The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to study intervention discontinuation. Duration of response will be derived using while on-treatment MRI volumetric assessments. |
| To demonstrate the effectiveness of selumetinib by assessment of PFS in participants with NF1 who have symptomatic, inoperable PN. | Progression free survival is defined as the time from the date of first selumetinib dose until date of progression by ICR per REiNS criteria or death (due to any cause). The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib. Progression free survival will be derived using while on-treatment MRI volumetric assessments. |
| To demonstrate the effectiveness of selumetinib by assessment of TTP in participants with NF1 who have symptomatic, inoperable PN. | Time to progression is defined as the time from the date of first selumetinib dose until date of documented objective disease progression by ICR per REiNS criteria. The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib. Time to progression will be derived using while on-treatment MRI volumetric assessments. |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To demonstrate the effectiveness of selumetinib by assessment of TTR in participants with NF1 who have symptomatic, inoperable PN. | Time to response is defined as the time from date of first selumetinib dose until the date of first documented objective response (which is subsequently confirmed), by ICR per REiNS criteria. The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR and who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to selumetinib discontinuation. Data obtained from first dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of TTR. Time to response will be derived using while on-treatment MRI volumetric assessments. |
| To demonstrate the effect of selumetinib relative to placebo by assessment of percentage change from baseline in target PN volume in participants with NF1 who have symptomatic, inoperable PN. | Difference in best percentage change from baseline in target PN volume by ICR per REiNS criteria between selumetinib and placebo during the randomised period. The analysis will include all participants randomised to study intervention with measurable target PN at baseline per ICR. The best percentage change from baseline in target PN volume will be derived using while on-treatment MRI volumetric assessments during the randomised period. |

## Table 4 Objectives and Endpoints

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To compare the effect of selumetinib relative to placebo by assessment of chronic target PN pain palliation and time to chronic target PN pain palliation in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline. | Chronic target PN pain palliation is defined as improvement of ≥ 2 in average cycle PAINS-pNF chronic target PN pain intensity score and no increase in chronic PN pain medication compared to baseline for that cycle. Pain palliation will be assessed in participants with a PAINS-pNF chronic target PN pain score of ≥ 3 at baseline.<br>• Difference in proportion of participants with chronic target PN pain palliation between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period.<br>• Time to chronic target PN pain palliation is defined as the time from the first dose of study drug until the cycle of chronic target PN pain palliation. |
| To compare the effect of selumetinib relative to placebo by assessment of pain medication compared with baseline. | Difference in change from baseline in pain medication use (as reported using the eDiary and as assessed by the investigator) between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by assessment of pain interference compared with baseline. | Difference in change from baseline in PII-pNF pain interference total score between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by assessment of physical functioning compared with baseline. | Difference in change from baseline in PROMIS Physical Function scores between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To compare the effect of selumetinib relative to placebo by further assessment of HRQoL compared with baseline. | Difference in change from baseline in the Skin Sensations domain from the PedsQL (NF1 module acute Version 3.0 – adult report) between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To compare the effect of selumetinib relative to placebo by assessment of health status compared with baseline. | Difference in change from baseline in EQ-5D-5L between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| | Difference in change from baseline in EQ-VAS between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To evaluate the effect of selumetinib by assessment of physical functioning compared with baseline. | Change from baseline in PROMIS Physical Function items. |
| To evaluate the effect of selumetinib by assessment of HRQoL compared with baseline. | Change from baseline in PlexiQoL. |
| | Change from baseline in the Skin Sensations domain from the PedsQL (NF1 module acute Version 3.0 – adult report). |
| To evaluate the effect of selumetinib by assessment of health status compared with baseline. | Change from baseline in EQ-5D-5L (standardised measure of health status). Five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). |
| | Change from baseline in EQ-VAS. |
| To assess the PK of selumetinib. | • Plasma concentrations and PK parameters of selumetinib including, but not limited to:<br>° Cmax, AUC(0-6), AUC(0-8), AUClast, CL/F, Vss/F, tmax, tlast derived after multiple dose administration.<br>• Plasma concentrations and PK parameters of N desmethyl selumetinib including, but not limited to:<br>° Cmax, AUC(0-6), AUC(0-8), AUClast, tmax , tlast derived after multiple dose administration.<br>° MPAUC and MPCmax after multiple dose administration.<br>• Population PK-pharmacodynamic analyses will be completed to investigate the selumetinib exposure-response relationship for safety and efficacy. The analyses will be reported separately from the Clinical Study Report. |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| **Safety** | |
| To assess the safety and tolerability of selumetinib alone and as compared to placebo in adult participants with NF1 who have symptomatic, inoperable PN. | Safety and tolerability will be evaluated in terms of AEs, vital signs, clinical laboratory assessments, urinalysis, physical exam, ECG (as clinically indicated), ECHO/cardiac MRI and ophthalmologic assessment. The safety analysis will include all randomised participants who receive at least one dose of study intervention.<br>Assessments related to AEs cover:<br>• Occurrence/Frequency<br>• Relationship to IP as assessed by investigator<br>• CTC grade<br>• Seriousness<br>• Death<br>• AEs leading to discontinuation of IP<br>• Other action taken related to IP<br>• AEs of special interest<br>• Other significant AEs<br>Vital signs parameters include systolic and diastolic BP, and pulse rate, respiration rate, oxygen saturation, body temperature and body weight.<br>Assessments cover:<br>• Observed value<br>• Absolute change from baseline values over time<br>Laboratory parameters include clinical chemistry and haematology parameters as well as urinalysis.<br>Assessments cover:<br>• Observed value<br>• Absolute change from baseline values over time<br>Echocardiogram/cardiac MRI assessments include measurement of LVEF.<br>Assessments cover:<br>• Observed value<br>• Absolute change from baseline values over time<br>Ophthalmologic assessments include best corrected visual acuity, IOP, and slit-lamp fundoscopy.<br>Assessments cover:<br>• Observed value |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| **Exploratory** | |
| To evaluate PFS during the randomised period on selumetinib and placebo in participants with NF1 who have symptomatic, inoperable PN. | Progression free survival is defined as the time from the date of first dose until date of progression by ICR per REiNS criteria or death (due to any cause).<br>The analysis will include all randomised participants.<br>Progression free survival will be derived using while on-treatment MRI volumetric assessments. |
| To compare the effect of selumetinib relative to placebo by assessment of spike target PN pain intensity. | Difference in change from baseline in PAINS-pNF spike target PN pain intensity between selumetinib and placebo at post-baseline cycles and overall over the randomised treatment period. |
| To explore potential biomarkers in residual biological samples, which may influence the progression of NF1 and inoperable PN (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 is not limited to) change from baseline in the expression and activity of NF1 and MEK pathways and/or specific RNA transcripts (arrays) as a surrogate for protein expression. |
| **The following exploratory objectives will be assessed over the entire duration of the study in all participants** | |
| To evaluate effect of selumetinib by assessment of chronic target PN pain intensity compared to baseline. | Change from baseline in PAINS-pNF chronic target PN pain intensity score. |
| To evaluate effect of selumetinib by assessment of spike target PN pain intensity compared to baseline. | Change from baseline in PAINS-pNF spike target PN pain intensity score. |
| To evaluate effect of selumetinib by assessment of chronic target PN pain palliation in participants with a PAINS-pNF chronic target PN pain score of $\geq 3$ at baseline. | Chronic target PN pain palliation is defined as improvement of $\geq 2$ in average cycle PAINS-pNF chronic target PN pain intensity score and no increase in chronic PN pain medication compared to baseline for that cycle. Pain palliation will be assessed in post baseline cycles in participants with a PAINS-pNF chronic target PN pain score of $\geq 3$ at baseline. |
| To evaluate effect of selumetinib by assessment of pain interference compared to baseline. | Change from baseline in PII-pNF pain interference total score. |
| To evaluate effect of selumetinib by assessment of pain medication compared to baseline. | Change from baseline in pain medication:<br>• As reported using the e-Diary. |

**Table 4 Objectives and Endpoints**

| Objectives | Estimands descriptions/Endpoints |
|---|---|
| To evaluate the efficacy of selumetinib based on NF1 mutation alteration patterns | Differences in ORR, PN pain intensity in subgroups if feasible based on NF1 mutation alteration patterns |
| **Exploratory endpoints assessed after end of Cycle 24 in fed conditions** | |
| To evaluate efficacy under fed dosing of selumetinib | Percentage change from baseline in target PN volume at Cycle 30 and 36. |

AE, adverse event; AUC(0-6), area under the concentration-time curve from time 0 to 6 hours; AUC(0-8), area under the concentration-time curve from time 0 to 8 hours; AUClast, area under the concentration-time curve from time 0 to time of last quantifiable concentration; BP, blood pressure; CL/F, apparent total body clearance of the drug from plasma after extravascular administration; Cmax, maximum observed concentration; CR, complete response; CTC, Common Terminology Criteria; DoR, duration of response; ECG, electrocardiogram; ECHO, echocardiogram; EQ-5D-5L, EuroQol 5-Dimension 5-level; EQ-VAS, EuroQol visual analogue scale; HRQoL, health related quality of life; ICR, independent central review; IOP, intraocular pressure; IP, investigational product; LVEF, Left ventricular ejection fraction; MEK, Mitogen activated protein kinase; MPAUC, Metabolite: parent ratio based on AUC; MPCmax, Metabolite:parent ratio based on Cmax; MRI, magnetic resonance imaging; NF1, Neurofibromatosis type 1; ORR, Objective response rate; PAINS-pNF, PAin INtensity Scale for Plexiform Neurofibromas; PedsQL, Paediatric Quality of Life Inventory; PFS, Progression free survival; PII-pNF, Pain interference index – plexiform neurofibroma; PK, pharmacokinetic(s); PlexiQoL, Plexiform Neurofibroma Quality of Life scale; PN, Plexiform neurofibroma(s); PR, partial response; PROMIS, Patient-Reported Outcomes Measurement Information System; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; RNA, Ribonucleic acid; tlast, time of last observed concentration; tmax, time to reach maximum observed concentration following drug administration; TTP, time to progression; TTR, time to response; Vss/F, volume of distribution (apparent) at steady state after extravenous administration.

# 4 STUDY DESIGN

## 4.1 Overall Design

This is a Phase III, multicentre, international study with a parallel, randomised, double-blind, placebo-controlled, 2 arm design to assess the efficacy and safety of selumetinib in adult participants with NF1 who have symptomatic, inoperable PN.

The study is intended to represent the population of adult patients with NF1 who have symptomatic, inoperable PN. Approximately 146 adult participants will be randomised who have NF1 and inoperable PN that cause symptoms including, but not exclusively, pain, disfigurement, airway impairment, and motor or bowel and/or bladder dysfunction. In order to achieve the global target of randomising 146 participants, this study will enrol approximately 212 participants at approximately 46 sites across 13 countries.

During screening, a single target PN will be selected by the Investigator and is defined as the clinically most relevant PN, which has to be measurable by volumetric MRI analysis (ie, a PN of at least 3 cm measured in one dimension, which can be seen on at least 3 imaging slices, and has a reasonably well-defined contour). If there is a second PN that is also considered clinically relevant and is measurable, the investigator may select this as a non-target PN; only one non-target PN can be selected.

As PNs are often associated with multiple co-morbidities such as pain and motor dysfunction, these elements will be assessed using various patient-reported outcome tools.

Pain, associated with the target PN, will be assessed using the PAINS-pNF, a modified NRS-11 pain scale for use in NF1-PN that measures the participant's usual chronic tumour pain as well as sudden bursts of tumour pain that may occur, known as spikes of tumour pain.

Chronic PN pain and spike pain medication use will be assessed during the study and all participants should have stable chronic PN pain medication use at baseline, as assessed by the investigator. Stable chronic PN pain medication is defined as no clinically significant changes to prescribed chronic PN pain medication within 28 days prior to study enrolment or planned at the time of study enrolment. All participants will be expected to complete PN pain intensity assessments using the eDiary in the screening period. During this time, participants must complete their pain diary for at least 4 days out of 7 days for at least 2 weeks in order to determine the participant's average baseline chronic target PN pain intensity score which is required for stratification.

Following a screening period lasting up to 28 days, approximately 146 eligible adult participants will be randomised in a 1:1 ratio to one of the following intervention groups:

- Arm A: selumetinib 25 mg/$m^2$ orally bid
- Arm B: placebo orally bid

Randomisation will be stratified by average baseline PAINS-pNF chronic target PN pain score and geographical region. The number of participants randomised will be capped at approximately 106 participants with an average baseline PAINS-pNF chronic target PN pain score ≥ 3 and approximately 40 participants with an average baseline PAINS-pNF chronic target PN pain score < 3.

Participants randomised to selumetinib will receive selumetinib 25 mg/$m^2$ orally bid (based on BSA, capped at 50 mg bid when BSA is ≥ 1.9 $m^2$) in 28-day cycles until a selumetinib discontinuation criterion is met. Participants randomised to placebo will receive placebo orally bid and will be crossed over to selumetinib treatment after the end of Cycle 12. Selumetinib capsules will be administered using BSA-based dosing. If it is anticipated that 20% or more of participants (across blinded study intervention groups) withdraw prior to the end of Cycle 16, for reasons other than progression, then recruitment rates withstanding, enrolment will continue to randomise at least 50% of the total number of drop-out participants to ensure the primary endpoint is adequately powered.

The interim analysis (DCO1) will occur after the 100th randomised participant has had the opportunity to complete their end of Cycle 16 assessment and the primary analysis (DCO2) will occur after the last participant dosed (the last participant receiving first dose) has had the opportunity to complete their end of Cycle 16 assessment. If the interim analysis DCO (DCO1) is due to take place within approximately 4 months of the primary analysis DCO (DCO2), then the interim analysis may not be performed and only the primary analysis will be performed. The primary analysis of ORR will take place at the end of Cycle 16 landmark and will be assessed in all randomised participants with measurable target PN at baseline per ICR. The summary measure of the 1st key secondary endpoint is the difference in the mean change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib compared to placebo. This will be assessed in participants with a PAINS-pNF chronic target PN pain intensity score of ≥ 3 at baseline and at least one postbaseline average cycle PAINS-pNF chronic target PN pain intensity score. The summary measure of the 2nd key secondary endpoint is the difference in the mean change from baseline in PlexiQOL total score at Cycle 12 between selumetinib compared to placebo. This will be assessed in participants with a baseline PlexiQOL total score and at least one post-baseline PlexiQOL total score.

The final analysis (Final DCO) will occur approximately 24 cycles post last participant dosed. The proposed duration for the study is approximately 24 months from last participant dosed to provide mature efficacy data as well as further safety and tolerability data. 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 and in the absence of discontinuation criteria.

As each participant reaches the end of Cycle 24 (Cycle 25 Day 1), they will then be permitted to eat at any time point in relation to each selumetinib intake. Since participants will be not require continuing to observe the fasting restriction, they will be considered in fed state. The data obtained in the fed state will be analysed in line with the main study analysis. Refer to Section 5.2.1 for the definition of participant fed state.

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

After study intervention discontinuation, all participants will undergo an end-of-treatment visit and will be followed up for safety assessments 30 (+ 7) days after their last dose of study intervention (ie, the safety follow-up visit), unless EoT is performed more than 30 days after last treatment dose, then the EoT assessments can also function as the 30-Day Safety follow-up visit.

## 4.2 Scientific Rationale for Study Design

Selumetinib has been shown to be effective in the treatment of paediatric patients with NF1 who have symptomatic, inoperable PN and is approved in the US for the treatment of paediatric patients aged ≥ 2 years of age. Plexiform neurofibromas, whilst typically present at birth, can continue to manifest through late adolescence and early adulthood (Williams et al 2009) and are often associated with significant clinical symptoms including pain and motor dysfunction (Gross et al 2018). As spontaneous resolution of symptoms associated with PN has been shown to be extremely unlikely (Gross et al 2018), adults with NF1-PN continue to have a significant unmet need. This study will aim to inform the benefit risk profile of selumetinib in adults with NF1 who have symptomatic, inoperable PN.

In the proposed study, the primary endpoint, ORR by end of Cycle 16, is assessed using volumetric MRI as determined by ICR per REiNS criteria. The REiNS expert group recommended volumetric MRI analysis as the most appropriate method to sensitively and reproducibly evaluate changes in PN size in clinical trials (Dombi et al 2013). It has been previously established in a longitudinal natural history study of NF1-PNs carried out by the

NCI that whilst some gradual spontaneous PN shrinkage from maximal tumour volume occurred, this was only in a small number of PNs (8.8%) with no PN having ≥ 20% shrinkage per year (Akshintala et al 2020). Given that median TTR in adult patients is approximately 10 months (O'Sullivan Coyne et al 2020), at least 16 cycles of follow-up is required to perform a meaningful comparison of ORR on selumetinib versus placebo. A limited placebo-controlled period (12 cycles) will be used in this study, which is considered an acceptable duration and still allows a robust comparison of ORR between treatment arms by end of Cycle 16 landmark.

Based on feedback from patients and KOLs, symptom improvement as well as tumour shrinkage is of primary importance for adults with NF1-PN. Since PN-related pain is a frequently reported symptom (O'Sullivan Coyne et al 2020) it is considered that reduction in pain would be a key treatment benefit. In the SPRINT paediatric study PN pain improvement (mean reduction in NRS-11 PN pain score of ≥ 2 compared with baseline in those with an NRS-11 PN pain score of ≥ 3 at baseline) was observed after 2 cycles. Therefore, a randomised period until the end of Cycle 12 was considered to be sufficient length to show reliable and lasting treatment effect in terms of PN pain improvement. The rationale for randomising approximately 106 participants with an average baseline PAINS-pNF chronic target PN pain score ≥ 3 (documented by daily completion during the screening period) is to ensure that sufficient participants are symptomatic for chronic PN pain at study entry; therefore, participants have an opportunity to achieve a clinically significant pain severity reduction.

Overall, the study is designed to show both tumour shrinkage and symptom improvement in adult participants with symptomatic, inoperable PN. Participants may have a variety of PN-related symptoms at baseline including but not limited to PN pain; approximately 106 participants with a baseline chronic target PN-related pain score of ≥ 3 will be randomised to enable analysis of chronic target PN-related pain as a key secondary objective. The 1st key secondary endpoint will be tested on participants with a PAINS-pNF chronic target PN pain intensity score of ≥ 3 at baseline as these participants have the capacity to show clinically meaningful improvement in PN pain.

### 4.2.1 Participant Input into Design

Interviews were conducted with a small group of adult patients with NF1 who have symptomatic PN to further understand the experience for adult patients with NF1-PN and this information was used to help inform the overall study design.

## 4.3 Justification for Dose

The safety profile of selumetinib has been established in adult patients with advanced cancers when given as monotherapy. The maximum tolerated dose of selumetinib in patients with advanced cancer is 75 mg bid as hyd-sulfate capsules. Dose escalation of selumetinib was

limited principally by the occurrence of rashes and diarrhoea.

A selumetinib dose of 25 mg/m$^2$ bid was used in the SPRINT study and is the currently approved dose in the US for paediatric patients aged 2 years and older. Based on the SPRINT study, selumetinib has a flat dose-exposure-response relationship for efficacy and safety across the 20 to 30 mg/m$^2$ bid dose range.

In adult healthy subjects, selumetinib exposure was higher in Asian subjects compared to non-Asians. Systemic exposure (dose normalised AUC and Cmax) of selumetinib in Chinese healthy subjects were a little higher (approximately 1.4-fold) than that in Western subjects. However, lower differences were shown when comparing body weight or BSA-normalised PK parameters. The geometric mean ratio (90% CI) of the AUC and Cmax, normalised by dose and body weight between the Chinese and Western population were 1.19 (1.03, 1.38) and 1.17 (0.92, 1.48), respectively. Similarly, the differences in mean PK exposure (AUC and Cmax) between Japanese and Western subjects were reduced from approximately 1.6 to 1.8-fold higher to approximately 1.4- to 1.7-fold higher after body weight or BSA normalisation.

In population PK analysis, more than race/ethnicity, BSA was identified as the significant covariate contributing to selumetinib clearance and volume of distribution. In addition to BSA, race (Asian or non-Asian) was correlated to clearance and hence AUC. The clinical impact for a typical Asian individual (29-years-old, BSA of 1.8 m$^2$) compared to a typical White patient of 10 years old with BSA of 1 m$^2$ was less than 20% for CL. As this is an international study with Asian participants, 25 mg/m$^2$ bid (already shown to be efficacious in paediatric patients) will provide similar exposure across ethnicities and across the global adult population.

Selumetinib, in adult patients with NF1 and inoperable PN, is being evaluated in an ongoing, Phase II paired-biopsy study (NCT02407405) sponsored by the NCI. This is an open-label, single-arm, single-site study in up to 35 evaluable patients evaluating the efficacy, pharmacodynamics, and tolerability of selumetinib. As of the DCO of 21 February 2020, 27 of 35 planned patients had been enrolled. A 75 mg bid fixed dose was not tolerated; the first 2 patients enrolled experienced Grade 3 acneiform rash despite maximum supportive care measures; one also developed Grade 3 scalp pain. The dose was reduced to 50 mg bid fixed dosing for all patients dosed subsequently.

Preliminary results show that treatment with selumetinib yields an interim ORR of 50% and improved patient reported pain intensity. Treatment resulted in pERK suppression in tumour biopsies, consistent with the mechanism of action. Selumetinib was well tolerated with a safety profile similar to that already established in paediatric patients with NF1 and adult patients with different cancers, and with strong evidence of clinical benefit and objective response in adults. Preliminary results from the study were presented at ASCO 2020

(O'Sullivan Coyne et al 2020).

In the study described in this CSP, participants will receive selumetinib 25 mg/m$^2$ orally bid based on BSA (capped at 50 mg bid when BSA is ≥ 1.9 m$^2$) rather than the 50 mg bid fixed dose irrespective of BSA that was used in the adult NF1 NCI study. This individualised BSA approach moderates exposure differences amongst ethnic groups. This also aligns with the BSA dosing approach used in the paediatric population, where patients continue to be dosed according to BSA if they continue treatment into adulthood.

## 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 the last scheduled visit shown in the SoA.

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

The end of the study is defined as the date when the last participant has completed their last scheduled visit (last participant last visit).

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

## 4.5 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 SARSCoV-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 AstraZeneca 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, HCP 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 AstraZeneca 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 minimise 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, and guidance on COVID-19 vaccine administration refer to Appendix K.

Note: In Germany the extent of these actions described above is restricted to the COVID-19 pandemic only; duties overseen by the PI will not be delegated to Health Care Providers

(HCP)/Third Party Vendors (TPV) and there will be no verbal consenting. Consent should be obtained in written format.

# 5 STUDY POPULATION

The target population of interest in this study is participants with NF1 who have symptomatic, inoperable PN.

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

Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.3.

## 5.1 Inclusion Criteria

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

**Age**

1 Participant must be ≥ 18 years at the time of screening.

**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 et al 2021):

(i) Six or more café-au-lait spots (> 5 mm in greatest diameter in pre-pubertal participants or > 15 mm in greatest diameter in post-pubertal participants)

(ii) Freckling in the axillary or inguinal region
- At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral

(iii) Two or more iris Lisch nodules identified by slit lamp examination or 2 or more choroidal abnormalities—defined as bright, patchy nodules imaged by optical coherence tomography/near-infrared reflectance imaging

(iv) Optic pathway glioma

(v) A distinctive osseous lesion such as: sphenoid dysplasia, anterolateral bowing of the tibia, or pseudoarthrosis of a long bone
- Sphenoid wing dysplasia is not a separate criterion in case of an ipsilateral orbital PN.

(vi) A NF1 heterozygous pathogenic variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells

(vii) A parent with NF1 by the above criteria

(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 2 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 (including significant bleeding or damage to nerves and/or surrounding vital structures) 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 caused by the PN, as judged by the investigator; symptoms may include, but are not limited to, pain, motor dysfunction, and disfigurement.

3 Participants must have completed a pain diary (PAINS-pNF) with a documented chronic target PN pain score for at least 4 days out of 7 days for at least 2 weeks during the screening period. Participants must have stable chronic PN pain medication use at baseline, defined as no clinically significant changes to prescribed chronic PN pain medication within 28 days prior to study enrolment or planned at the time of study enrolment.

4 Eastern Cooperative Oncology Group performance status of 0 or 1 with no deterioration over the previous 2 weeks prior to baseline or day of first dosing. Participants who are wheelchair bound because of paralysis secondary to a PN should be considered ambulatory when they are in their wheelchair. Similarly, participants with limited mobility secondary to a need for mechanical support (such as an airway PN requiring tracheostomy or continuous positive airway pressure) will also be considered ambulatory for the purpose of the study.

5 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 measurable by volumetric MRI analysis.

6 Adequate organ and marrow function as follows with no blood transfusions (of red blood cells/other blood products) within 28 days prior to screening assessment and no growth factors within 7 days prior to screening assessment:

- Haemoglobin $\geq 9.0$ g/dL.
- Absolute neutrophil count $\geq 1.5 \times 10^9$/L.

- Platelet count ≥ 100 × $10^9$/L.
- Total bilirubin ≤ 1.5 × ULN or ≤ 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinemia).
- Alanine aminotransferase and AST ≤ 2.5 × ULN.
- Calculated creatinine clearance ≥ 60 mL/min as determined by Cockcroft-Gault (using actual body weight).

  Males:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

  Females:

  $$\text{CrCL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

7 All participants must be able to swallow whole capsules.

**Sex**

8 Male or female.

**Reproduction**

9 Negative pregnancy test (serum) for women of childbearing potential.

10 Female participants must be one year post-menopausal, surgically sterile, or using one highly effective form of birth control (a highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly). Women of childbearing potential must agree to use one highly effective method of birth control. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the study and until at least one week after the last dose (see Appendix F for complete list of highly effective birth control methods). Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period and until at least one week after the female participant's last dose of study intervention. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant.

11 Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception

such as male condom plus spermicide (condom alone in countries where spermicides are not approved) (see Appendix F) from the time of screening throughout the total duration of the study and the drug washout period (at least one week after the last dose of study intervention) to prevent pregnancy in a partner. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Vasectomised (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study. Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study. Male participants must not donate or bank sperm during this same time period. Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period.

**Informed Consent**

12 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

13 Provision of signed and dated written Optional Genetic Research Information informed consent prior to collection of sample for optional genetic research that supports Genomic Initiative.

## 5.2 Exclusion Criteria

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

**Medical Conditions**

1 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diseases, and known moderate or severe hepatic impairment), or history of allogenic organ transplant, which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.

2 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.

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

4 History of malignancy except for malignancy treated with curative intent with no known active disease ≥ 5 years before the first dose of study intervention and of low potential risk for recurrence. Exceptions include basal cell carcinoma of the skin and squamous cell carcinoma of the skin that has undergone potentially curative therapy.

5 Persistent toxicities (CTCAE Grade ≥ 2) caused by previous therapy for NF1-PN, excluding hair changes such as alopecia or hair lightening. Participants with toxicity clinically considered to be irreversible (eg, hearing loss) that is not reasonably expected to be exacerbated by study intervention may be permitted.

6 Known active hepatitis infection, positive hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody, at screening. Testing is not required for assessment of eligibility for the study.

7 Known to have tested positive for HIV. Participants with HIV who have adequate CD4 count, not requiring antiretroviral medication, may be enrolled. Testing is not required for assessment of eligibility for the study.

8 Investigator judgment of one or more of the following:

(a) Mean resting QTcF interval >470 ms, obtained from triplicate ECGs performed at screening.

– History of QT prolongation associated with other medications that required discontinuation of that medication.

– Congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives.

9 Symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia. Participants with atrial fibrillation clinically well-controlled by medication may be permitted.

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

(a) Known inherited coronary disease

(b) Acute coronary syndrome within 6 months prior to starting treatment

(c) Uncontrolled angina – Canadian Cardiovascular Society Grade II to IV despite medical therapy (Appendix I)

(d) Symptomatic heart failure – New York Heart Association Class II to IV

(e) Prior or current cardiomyopathy

(f) Severe valvular heart disease

(g) Baseline LVEF below LLN or < 55% measured by ECHO or cardiac MRI

(h) Uncontrolled hypertension (at screening: BP ≥ 140/90 despite optimal therapy)

11 Participants with the following ophthalmological findings/conditions:

(a) Current or past history of RPED/CSR or RVO

(b) 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.

(c) Participants with any other significant abnormality on ophthalmic examination should be reviewed for potential eligibility.

(d) 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.

12 Inability to undergo MRI and/or contraindication for MRI examinations. Prosthesis or orthopaedic or dental braces in close proximity to the area of interest that would interfere with volumetric analysis of target PN on MRI.

**Prior/Concomitant Therapy**

13 Prior exposure to MEK inhibitors.

14 Receipt of the last dose of systemic PN target treatment (including chemotherapy, immunotherapy, targeted therapy, biologic therapy, or monoclonal antibodies) within 4 weeks prior to the first dose of study intervention or 5 half-lives of the respective systemic PN target treatment, whichever is longer.

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

16 Major surgical procedure (excluding placement of vascular access) or significant traumatic injury within 4 weeks of the first dose of study intervention or an anticipated need for major surgery during the study.

17 Receiving herbal supplements or medications at doses known to be strong or moderate inducers of CYP3A4 unless such products can be safely discontinued at least 14 days or 5 half-lives (whichever is longer) before the first dose of study intervention (see Appendix J).

18 With the exception of chronic PN pain medication, receiving herbal supplements or medications at doses known to be strong or moderate inhibitors of the CYP2C19 and CYP3A4 enzymes, unless such products can be safely discontinued at least 14 days or 5 half-lives (whichever is longer) before the first dose of study intervention (see Appendix J).

19 Any multivitamin containing vitamin E must be stopped at least 7 days prior to initiation of study intervention.

**Prior/Concurrent Clinical Study Experience**

20 Previous treatment in the present study.

21 Participation in another clinical study with a study intervention or investigational medicinal device administered in the last 4 weeks or 5 half-lives, whichever is longer, prior to first dose of study intervention or concurrent enrolment in another clinical study,

unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

22 Participants with a known hypersensitivity to selumetinib or any of the excipients of the product.

**Other Exclusions**

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

24 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. This includes investigator judgement that the participant will not be able to adequately understand or consistently complete electronic PRO instruments.

25 Currently pregnant (confirmed with positive pregnancy test), intending to become pregnant, or breast feeding (lactation must be discontinued throughout the period of the study and until at least one week after the last dose of study intervention).

**Lifestyle Considerations**

The following restrictions apply while the participant is receiving study intervention and for the specified times before and after:

1 Participants must follow the contraception requirements outlined in Appendix F.

2 Participants should not donate blood or blood components while participating in this study and through 12 weeks after the last dose of study intervention.

Restrictions relating to concomitant therapies are described in Appendix J 2.

### 5.2.1 Meals and Dietary Restrictions

Study intervention capsules should be swallowed whole with a glassful of water twice a day, approximately 12 hours apart (but no less than 6 hours apart), on an empty stomach (no food or drink other than water for 2 hours prior to dosing and one hour after dosing).

Participants should refrain from consumption of Seville oranges, grapefruit or grapefruit juice, from 7 days before the start of study intervention until after the final dose.

From the end of Cycle 24 (Cycle 25 Day 1) participants will not be required to continue to observe the fasting restriction described above, meaning that participant can eat at any time point in relation to each selumetinib intake.

A participant is defined to switch to the fed state from the moment after the end of Cycle 24 (Cycle 25 Day 1) when the participant is no longer required to continue to observe the fasting

restriction and can eat at any time point in relation to each selumetinib intake. The participants who reach the end of Cycle 24 prior to the approval of the third protocol amendment will be considered in fed state from the timepoint when they will reconsent to participate in the study without the fasting restriction and the date of their ICF signature after Cycle 25 Day 1 will be the start date of the fed state.

### 5.2.2 Alcohol

On each PK day, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.

### 5.2.3 Activity

Participants should be made aware of the need for good oral care during studies with selumetinib due to possible risk of oral mucositis and dry mouth (see Appendix H 7 for more detail).

## 5.3 Screen Failures

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

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time if the screening failure was due to a temporary condition. Participants who screen fail based on PN pain intensity assessment cannot be rescreened unless it is due to a technical reason (ie, e-Diary device not synching with system used to enroll the participant). Rescreened participants should be assigned the same participant number (ie, E-code) as for the initial screening. Participants should be rescreened once sufficient time has elapsed to feasibly allow correction of the reason for screen failure. However, rescreening should be documented so that its effect on study results, if any, can be assessed. All assessments must be repeated for rescreening unless they are within 28 days of randomisation.

These participants should have the reason for study withdrawal recorded in the eCRF as “screen failure” (ie, participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, participants who are not randomised in the study).

Participant enrolment and randomisation is described in Section 6.3.

# 6 STUDY INTERVENTION

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

## 6.1 Study Intervention(s) Administered

### 6.1.1 Investigational Products

AstraZeneca will supply selumetinib and placebo capsules. It will be sent blinded and unblinded to the site; blinded label stock will be provided to participants prior to crossover and following crossover, unblinded, open label stock will be dispensed to the participant.

Dose modifications are described in Section 6.6.

**Table 5 Investigational Products**

| | | |
|---|---|---|
| **ARM name** | Arm A | Arm B |
| **Intervention name** | Selumetinib | Placebo |
| **Type** | Drug | Drug |
| **Dose formulation** | Capsule | Capsule |
| **Unit dose strength(s)** | 10 mg and 25 mg capsules | Placebo to match selumetinib 10 mg and 25 mg capsules |
| **Dosage level(s)** | 25 mg/m$^2$ bid – see BSA dosing table below. | Placebo 25 mg/m$^2$ bid – see BSA dosing table below. |
| **Route of administration** | Oral | Oral |
| **Use** | Experimental | Placebo |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | Provided centrally by AstraZeneca | Provided centrally by AstraZeneca |
| **Packaging and labelling** | Selumetinib 10 mg (white) and 25 mg (blue) capsules in 60 count bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GCP Ordinance. | Matching placebo (white and blue) capsules in 60 count bottles. Each bottle will be labelled in accordance with Good Manufacturing Practice Annex 13 and per country regulatory requirement. Labels will be prepared in accordance with GCP Ordinance. |
| **Current/former name(s) or alias(es)** | AZD6244 | N/A |

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

**Table 6 Body Surface Area Dosing Guidelines**

| Body surface area ($m^2$) | Selumetinib starting dose (mg) [a] | |
|---|---|---|
| | AM | PM |
| 1.1 to 1.29 | 30 | 30 |
| 1.3 to 1.49 | 35 | 35 |
| 1.5 to 1.69 | 40 | 40 |
| 1.7 to 1.89 | 45 | 45 |
| ≥ 1.90 | 50 | 50 |

[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.

Study intervention capsules should be swallowed whole with a glassful of water twice a day, approximately 12 hours apart but no less than 6 hours apart, on an empty stomach (no food or drink other than water for 2 hours prior to dosing and one hour after dosing).

From the end of Cycle 24 (Cycle 25 Day 1) participants will not be required to continue to observe the fasting restriction described above, meaning that the participant can eat at any time point in relation with each selumetinib intake Participants will be therefore considered in fed state Refer to Section 5.2.1 for the definition of participant fed state.

If a dose of study treatment is missed, it should only be taken if it is more than 6 hours until the next scheduled dose. If vomiting occurs after study treatment administration, an additional dose should not be taken. Dosing should be continued with the next scheduled dose.

**Selumetinib**

Participants in the selumetinib group will receive 25 mg/$m^2$ selumetinib as oral capsules bid. Dosing will be based on BSA and capped at 50 mg bid when BSA is ≥ 1.9 $m^2$.

**Placebo**

Participants in the placebo group will receive placebo as oral capsules bid.

**Duration of Treatment**

Participants in the selumetinib group will receive 25 mg/$m^2$ selumetinib as oral capsules bid until a selumetinib discontinuation criterion is met. Participants in the placebo group will receive placebo as oral capsules bid until the end of Cycle 12 and then will cross over to selumetinib treatment.

Crossover within the study will be permitted. Participants in the placebo group will crossover to receive selumetinib after the end of Cycle 12. However, if the investigator requests

unblinding due to suspected progression during the randomised period, and the request is deemed appropriate, the relevant MRI scans will be assessed by ICR, per REiNS criteria. Unblinding will only be permitted if the participant has progression on imaging as determined by ICR. If the participant was on placebo they will be allowed to crossover to selumetinib treatment. Following crossover to selumetinib treatment, subsequent treatment will be open-label.

Participants may continue to receive selumetinib beyond the final DCO as long as they are continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

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

## 6.2 Preparation/Handling/Storage/Accountability of Interventions

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

2 Only participants enrolled in the study may receive study intervention and only authorised site staff may supply or administer study intervention. All study intervention 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.

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

4 Further guidance and information for the final disposition of unused study interventions are provided in a separate document.

## 6.3 Measures to Minimise Bias: Randomisation and Blinding

**Participant Enrolment and Randomisation**

All participants will be centrally assigned to randomised study intervention using IRT. Before the study is initiated, login instructions for the IRT and/or login information and instructions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarised in Table 1.

Returned study intervention should not be re-dispensed to the participants.

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

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

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

- Obtain signed informed consent before any study-specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the participant. However, all screening laboratory and imaging results must have been obtained within 28 days of the first dose of study intervention.
- Participants will be identified to the IRT per country regulations. Obtain a unique 7-digit enrolment number (E-code), through the IRT in the following format (ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the participant enrolment code at the centre). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Obtain signed informed consent for genetic research study (optional). Participants who decide not to sign the specific genetic ICF, but the general study ICF, are eligible for study enrolment and all other study procedures.

At randomisation, once the participant is confirmed to be eligible, the investigator or suitably trained delegate will:

- Assign a randomised treatment group via IRT. Randomisation codes will be assigned strictly sequentially within each stratum as participants become eligible for randomisation. The system will randomise the eligible participant to one of the 2 treatment groups.

If the participant is ineligible and not randomised, the IRT should be accessed to terminate the participant in the system.

Participants will begin study intervention on Day 1. Participants must not be randomised and treated unless all eligibility criteria have been met.

**Procedures for Handling Incorrectly Enrolled or Randomised Participants**

Participants who fail to meet the eligibility criteria should not, under any circumstances, be

enrolled or receive study medication. 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 randomised or started on study intervention and must be withdrawn from the study.

Where a participant does not meet all the eligibility criteria but is randomised in error, or incorrectly started on study intervention, 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 study intervention. The AstraZeneca Medical Monitor must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

**Methods for Assigning Treatment Groups**

The actual treatment given to participants will be determined by the randomisation scheme in the IRT. The randomisation scheme will be produced by a computer software programme that incorporates a standard procedure for generating randomisation numbers. One randomisation list will be produced for each of the randomisation strata. A blocked randomisation will be generated, and randomisation will be balanced within the IRT at the central level.

Randomisation codes will be assigned strictly sequentially, within each stratum, as participants become eligible for randomisation. The IRT will provide the kit identification number to be allocated to the participant at the randomisation visit and subsequent treatment visits. For participants assigned to placebo at randomisation, the cross-over to selumetinib will occur after the end of Cycle 12. The switch will be programmed into the IRT system to allow the participant to receive selumetinib from that point forward.

**Methods for Ensuring Blinding**

| | |
|---|---|
| IRT | The IRT will provide to the investigator(s) or pharmacists the kit identification number to be allocated to the participant at the dispensing visit.<br>Routines for this will be described in the IRT user manual that will be provided to each centre.<br>The randomisation code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the study intervention randomisation. The investigator documents and reports the action to AstraZeneca, without revealing the study intervention given to participant to the AstraZeneca staff.<br>AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomisation codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented. |

| | |
|---|---|
| Blind break IRT | The IRT will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, AstraZeneca must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the study intervention given to participant to the AstraZeneca staff. Emergency unblinding will lead to the participant being discontinued from the study following EOT and Safety Follow-up Visits (see Section 7.2 for procedures for participant withdrawal from study).<br>The laboratory vendor personnel performing the bioanalysis of the plasma samples will have access to the randomisation list. |

EOT, end of treatment; IRT, Interactive Response Technology; SAE, serious adverse event.

## 6.4 Study Intervention Compliance

If participants are dosed at the site (eg, on PK assessment 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.

Participants will complete a daily drug diary to record whether study intervention was taken as instructed.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Study intervention compliance will be assessed by review of the daily drug diary, reconciliation of site drug accountability logs and by counting returned capsules during each site visit.

A record of the number of 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.

Deviation(s) from the prescribed dosage regimen should 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.

The investigator(s) is responsible for ensuring that the participant has returned all unused study intervention.

## 6.5 Concomitant Therapy

Any concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, 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 follow-up period 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 AstraZeneca 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.

Strong or moderate **inducers** of **CYP3A4** are not allowed at any time during the study. During the first cycle, concomitant use of strong or moderate **inhibitors of CYP3A4 or CYP2C19,** with the exception of chronic PN medication, should be avoided until after the PK assessment. If concomitant use of selumetinib with strong or moderate CYP3A4 or CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Appendix J Table J15. For chronic PN pain medication fulfilling the above criteria, selumetinib should be initiated at a reduced dose as shown in Appendix J Table J15. The dose of selumetinib should be reduced for the duration of concomitant therapy with the strong or moderate CYP3A4 or CYP2C19 inhibitors 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.

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 administered with caution.

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 not take any supplemental vitamin E. High doses of vitamin E have been reported to cause bleeding and interfere with blood coagulation processes. Selumetinib should be administered with caution in 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.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix J 2.

## 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 H.

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 AEs** (Appendix H):

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 7. If the AE does not resolve to CTCAE Grade 1 or less within 4 weeks of onset, study intervention must be permanently discontinued unless otherwise specified in the Guidance for Management of Specific AEs (Appendix H).

The dose modification procedure is shown in Table 7. 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 7. For example, if a participant has a BSA of 1.8 $m^2$ and starts on a dose of 45 mg bid and then has a dose reduction to 35 mg AM, 30 mg PM then a

subsequent BSA increase to 1.9 $m^2$ would mean the participant should be dose adjusted to 35 mg bid.

Note that if selumetinib is interrupted for more than 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 AstraZeneca 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 AstraZeneca Medical Monitor.

**Table 7 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 |
| ≥ 1.90 | 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 Intervention after the End of the Study

As described in Section 4.4, the study will remain open until the last participant has completed their last scheduled visit (last participant last visit).

After the final DCO for this study, AstraZeneca will continue to supply selumetinib to participants who received selumetinib until disease progression occurs as judged by the investigator or until meeting any other discontinuation criteria as defined in Section 7.1.

In the event that a roll-over or safety extension study is available at the time of the final DCO and database closure, participants currently receiving treatment with selumetinib may be transitioned to such a study, and the current study would 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 proposed to move to such a study would be given a new informed consent, as applicable.

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

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for 30 day safety follow-up. 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:

- 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 study intervention, without prejudice to further treatment. A participant who discontinues study intervention is normally expected to continue to participate in the study for the 30 day safety follow-up 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 or intent to become pregnant.
- Initiation of subsequent therapy for NF1-PN, including another investigational agent.
- Participants who experience disease progression based on the investigator’s decision.

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

Crossover within the study will be permitted (see Section 6.1.1 for details).

See the SoA (Table 1) for data to be collected at the time of intervention discontinuation (ie, the EoT visit) and follow-up and for any further evaluations that need to be completed.

### 7.1.1 Follow-up of Participants Post Discontinuation of Study Intervention

All participants who discontinue the study intervention will be followed up for safety assessments 30 days after their last dose of study intervention. Additional assessments to be performed at the time of the 30 day safety follow-up are detailed in the SoA (Table 1).

## 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. Emergency unblinding will also lead to the participant being discontinued from the study following EOT and Safety Follow-up Visits. 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 EoT visit should be conducted, as shown in the SoA. See SoA (Table 1) 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 the study intervention and be withdrawn from the study at that time.
- If the participant withdraws consent for disclosure of future information, AstraZeneca 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 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 no contact has been established by the time the study is completed (see Section 4.4).

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 protocol.

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 the participant 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 have been lost to follow-up from the study.

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 (Table 1 and Table 2). Data collection following study analysis until the end of the study is described below.

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with AstraZeneca 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) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

**Data Collection Following Study Analysis until the End of the Study**

Following the DCO2 for the primary efficacy endpoint, participants will continue with all assessments as indicated in the SoA.

For SAE and AE reporting and laboratory assessment collection after final analysis, see Section 8.3.11.

After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.3.11).

## 8.1 Efficacy Assessments

### 8.1.1 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. MRI 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. Prior to starting treatment on this study, the investigator must select a single target PN. The target PN is defined as the clinically most relevant PN, 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. Non-target PNs must also be measurable. AstraZeneca's appointed imaging CRO will measure the target PN and non-target PN (if applicable). However, 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 QC, 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 independent central review of images will be performed for the assessment of efficacy according to the REiNS criteria. In general, 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. However, if the investigator requests unblinding due to suspected progression during the randomised period, and the request is deemed appropriate, the relevant MRI scans will be assessed by ICR per REiNS criteria. Unblinding will only be permitted if the participant has progression on imaging as determined by ICR. If the participant was on placebo they will be allowed to crossover to selumetinib treatment.

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 1, 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 24 cycles. From the end of Cycle 24, tumour assessments will be performed every 6 cycles (24 ± 1 weeks), as long as the participant remains on study intervention. Volumetric MRI assessment of the target and non-target PNs according to the REiNS criteria will be performed by the central imaging vendor. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the participant has not progressed, the subsequent assessments at the next scheduled visit must be performed.

The REiNS criteria as assessed by volumetric MRI of the target PN performed by the ICR 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 PR is considered unconfirmed at the first detection and confirmed when observed again at a consecutive scan within 3 to 6 months.
- Stable disease: insufficient volume change to qualify for either PR or PD.
- 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.

Before submitting the MRI scans to the central review vendor site staff should ensure that the target PN and non-target PN (if applicable) are fully visible on the scans.

In the event that a participant taking part in the study had a target PN resection and remained in the study, MRI scans will continue to be collected.

### 8.1.2 Independent Central Review of Scans

Independent central review of scans will be conducted as described in Section 8.1.1. A double read of all MRI scans will be performed. The ICR reviewers will be blinded to study intervention group.

### 8.1.3 Objective Response Rate

Objective response rate is defined as the proportion of participants 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 PR (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.

### 8.1.4 Progression Free Survival

Progression free survival is defined as the time from the date of first selumetinib dose until date of progression by ICR per REiNS criteria or death (due to any cause).

### 8.1.5 Duration of Response

Duration of response will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression by ICR per REiNS

criteria or death due to any cause.

### 8.1.6 Time to Progression

Time to progression is defined as the time from the date of first selumetinib dose until date of documented objective disease progression by ICR per REiNS criteria.

### 8.1.7 Time to Response

Time to response is defined as the time from date of first selumetinib dose until the date of first documented objective response (which is subsequently confirmed), by ICR per REiNS criteria.

### 8.1.8 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. Clinical outcome assessments can be reported by a participant (PRO), a clinician (ClinRO), an observer (ObsRO), 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 health-related QoL of the participant to aid understanding of the risk-benefit profile.

A PRO is one type of COA and is a general term referring to all outcomes and symptoms that are directly reported by the participant. Patient reported outcomes have become important in evaluating the effectiveness of study interventions in clinical studies and will aid in understanding of the benefit/risk evaluation (EMA Guideline 2016, FDA Guidance for Industry).

The following PRO instruments will be administered in this study:

- Pain Intensity Plexiform Neurofibroma (PAINS-pNF)
- Pain Interference Index Plexiform Neurofibroma (PII-pNF)
- Patient reported Outcomes Measurement Information System (PROMIS physical function items)
- Plexiform Neurofibromas Quality of Life Measure (PlexiQoL)
- Paediatric Quality of Life Inventory (NF1 module acute Version 3.0 – adult report) Skin Sensations domain
- EuroQol 5-Dimension 5-level (EQ-5D-5L)
- Patients Global Impression of Change (PGIC)
- Patients GLOBAL Impression of Severity (PGIS)

Patient Reported Outcomes will be administered according to the SoA.

The ECOG performance status will also be assessed as a COA in this study.

Patient reported outcomes data collection will be discontinued after the participant discontinues study intervention.

#### 8.1.8.1 PAINS-pNF

The use of an NRS-11 measure is well established for measuring pain intensity (Atkinson et al 2010; Dworkin et al 2005; Wolters et al 2013; Wolters et al 2016). Pain intensity is considered a core concept that is important to assess in the NF1 population (Wolters et al 2013). The REiNS International Collaboration, after assessing PRO measures for pain in patients with NF1, recommended the NRS–11 for use in the assessment of pain intensity in patients aged ≥ 8 years (Wolters et al 2016). This measure was found to be both reliable and valid, and it is preferred over other measures such as the Visual Analogue Scale and the Faces Pain Scale-Revised because of its psychometric properties and wide use in clinical research (Wolters et al 2013). However, there is no NRS-11 measure specifically validated for patients with NF1-PN. To address this gap, the NCI is currently going through the qualification process with the PAINS-pNF Scale (FDA Drug Development Tool). The NCI is willing for its qualitative work to be used in support of the PAINS-pNF measure to be used in the proposed Phase III study in adult NF1-PN participants.

For this study, the PAINS-pNF which is a 'fit for purpose' measure for NF1-PN patients that is based on an NRS-11 scale will be used. The PAINS-pNF has 2 items, one assessing participants' experience of spikes of PN-related pain intensity (also known as episodic tumour pain), which are defined as sudden bursts of tumour pain that may occur spontaneously or in response to a stimulus and the other item is their experience of chronic PN-related pain intensity (also known as usual tumour pain), which is defined as tumour pain that is present most of the time, both for a target PN-location. Participants report pain intensity by selecting the number/integer from 0 (no tumour pain [spike]/no tumour pain [usual/chronic]) to 10 (worst tumour pain possible [spike]/worst tumour pain possible [usual/chronic]). In the event that a participant taking part in the study had a target PN resection and remained in the study, PAINS-pNF data will continue to be collected.

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

#### 8.1.8.2 PII-pNF

The PII-pNF assesses the extent to which PN pain interferes with daily functioning. All items ask the participant to consider the pain related to their PN in the past 7 days. Participants are asked how much their PN pain has made it hard for them to engage in physical activities (eg, challenging physical activities, self-care), affected their physiological processes (eg, sleep, energy) or impacted their social-emotional functioning (eg, enjoyment of activities,

mood). Items are rated on a 7-point Likert scale (0 = not at all to 6 = completely), and the total score is the mean of the completed items.

A copy of the scale is provided in Appendix G 2

#### 8.1.8.3 Pain Medication Assessment Diary

**Pain Medication e-Diary**

At the screening visit, the site staff will pre-populate the e-Diary on the handheld device with the pain medications that the participant uses for chronic PN pain, as well as any medications that they typically use for spikes of PN pain.

On a daily basis the participant will record on the e-Diary the pain medications that they have taken for their chronic PN pain and spikes of PN pain.

The participant should bring their handheld device to each site visit; the site staff will review if any changes need to be made to the pre-populated medications on the device.

**Investigator Assessment of Pain Medication**

At the frequency stipulated in the SoA, the investigator will record in the eCRF if the participant's analgesic requirement has changed compared to baseline since it was last assessed. This assessment will be made based on discussions with the participant and knowledge of any changes in their pain management. If the investigator determines that there has been a change, they will record if there has been an increase or decrease and the reason for this change.

#### 8.1.8.4 PROMIS

The Adult PROMIS Physical Functioning (PF) items scales measure self-reported capability rather than actual performance of physical activities. Items assess upper extremity function (dexterity), lower extremity function (walking or mobility), and central regions (neck, back) as well as activities of daily living such as running errands.

Participants will be assessed using selected items from the PROMIS item bank that map to physical function concepts relevant to patients with symptomatic PNs.

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

#### 8.1.8.5 PlexiQoL

The PlexiQoL is a patient-derived QoL measure specific to adults with NF1-associated PNs. It assesses the impact of PNs on patients' ability to fulfil their human needs. The scale adopts the needs -based model of QoL and joins a large portfolio of high-quality outcome measures that are widely used in international clinical trials (Heaney et al 2020).

The measure consists of 18 dichotomous items with 0 =”Not True” and 1 = “True”. Scores are summed to a maximum of 18, with lower scores indicating better quality of life.

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

#### 8.1.8.6 PedsQL (NF1 Module Acute Version 3.0 – Adult Report) Skin Sensations Domain

The adult version of PedsQL™ NF1 Module can be used to understand the multidimensional nature of NF1 on the HRQoL patients with this disorder and may assist in medical decision making. The instrument demonstrates initial feasibility, reliability, and discriminant validity. The PedsQL™ NF1 Module 3.0: Adult self-report instrument comprises 18 domains/subscales and participants will be assessed using the Skin Sensations domain (3 items) with a 7-day recall period (Nutakki et al 2013).

These are rated on a 5-point Likert scale from 0 (Never) to 4 (Almost always). Items are reversed scored and linearly transformed to a 0 to 100 scale as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0. Domain scores are calculated by the sum of all the items over the number of items answered.

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

#### 8.1.8.7 PGIC and PGIS

The global impressions of change for PN-related pain are self-reported measures that will be used to assess change in participant’s PN-related pain as follows:

- PGIC 1: ‘since your last visit to the study site’
- PGIC 2 ‘since starting the study medication’

The 2 PGICs will be used to evaluate the clinical significance of changes in PN-related spikes of pain and chronic pain on a 7-point scale (1 = Very much improved to 7 = Very much worse) (Guy 1976).

The global impression of severity for PN-related pain is a self-reported measure used to assess severity of participant’s PN-related pain. It is a global two-item measure and will be used to evaluate the clinical significance of PN-related spikes of pain and chronic pain severity on a 4-point scale (1 = No pain to 4 = Severe).

Copies of the scales are provided in Appendix G 6 (PGIC) and Appendix G 7 (PGIS).

#### 8.1.8.8 EQ-5D-5L

The EQ-5D-5L will be used to explore the impact of treatment and disease state on health state utility.

The EQ-5D-5L, developed by the EuroQoL Group, is a generic questionnaire that provides a simple descriptive profile of health and a single index value for health status for economic appraisal (EuroQol 2019). The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) over 5 levels of increasing severity ("no problems," "slight problems," "moderate problems", "severe problems", and "extreme problems"). Participants indicate their current health state by selecting the most appropriate level in each of the 5 dimensions.

Respondents also assess their health today using the EQ-VAS, which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

A copy of the scale is provided in Appendix G 8.

#### 8.1.8.9 Administration of ePRO Questionnaires

Participants will complete a daily e-Diary using a hand-held device at home to capture:

- PN pain intensity (assessed using the PAINS-pNF)
- PN pain medication use
- Drug diary to record whether study intervention was taken as instructed

For all other ePRO assessments including PII-pNF, PGIC, PGIS, PROMIS physical function items, PlexiQol, Peds QL (NF1 module-adult form) Skin Sensations domain, and EQ-5D-5L, participants will perform the ePRO assessments using an electronic tablet during clinic visits at the time points indicated in the SoA.

Each site must allocate the responsibility for the administration of the ePRO 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 PRO data via an electronic device:

- The PRO questionnaires should be completed prior to any other study procedures or discussions (following informed consent) that could bias the participant's responses to the questions.
- At site visits, when each instrument is due to be completed, the following order should be observed:
  - Patient Global Impression of Severity (PGIS)
  - Patient Global Impression of Change (PGIC)
  - Pain Interference Index Plexiform Neurofibroma (PII-pNF)

  - Patient reported Outcomes Measurement Information System (PROMIS physical function items)
  - Paediatric Quality of Life Inventory (PedsQL NF1 module acute Version 3.0 – adult report) Skin Sensations domain
  - Plexiform Neurofibromas Quality of Life Measure (PlexiQoL)
  - EuroQol 5-Dimension 5-level (EQ-5D-5L)

- The PRO questionnaires should be completed by the participant in a quiet and private location.
- The participant should be given sufficient time to complete the PRO questionnaires at his/her own speed.
- The research nurse or appointed site staff should explain to participants 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, he/she should discuss them with the doctor or research nurse separately from the ePRO assessment.
- The research nurse or appointed site staff must train the participant on how to use the ePRO 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 participant is completing the ePRO at home.
- All questionnaires must be completed using the ePRO device. Paper questionnaires may be allowed in this study under exceptional circumstances (eg, an IT system failure or breakage of electronic device).
- 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.
- The participant should not, wherever possible, receive help from relatives, friends, or clinic staff to read or complete the ePRO questionnaires. However, if the participant has motor or reading difficulties that will prevent them from using the e-Device, the items may be read aloud or responses selected on the e-Device. Any person providing assistance must be informed by site staff that they must not influence the participant's responses in any way and responses selected on the e-Device on behalf of the participant must follow the answer provided by the participant aloud.
- Site staff must administer 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 vital that the ePRO reporting is initiated as specified in the SoA to capture the effect of study intervention.
- Reminders should be sent to participants at home as needed to ensure compliance with the assessment schedules.
- 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 participant could not complete assessments, in the source documents and in the designated eCRF. If a participant's 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 participant to improve compliance, a check in call from the site to ask the participant if they have any difficulties in completing questionnaires on schedule, etc). Whilst site staff will be able to monitor compliance they will remain blinded to the PAINS-pNF scores (except in exceptional circumstances when paper copies are used).
- In the event that the ePRO device cannot be used (ie, technical failure, lost device, etc) and there is a back-up platform available for the PRO questionnaire, the participant will complete it on a website following the same steps as outlined above.

#### 8.1.8.10 Qualitative Participant Interviews

Qualitative interviews will be performed in approximately 36 trial participants at baseline and at 2 other timepoints during the trial. During the baseline interviews, trial participants will be asked a series of questions to better understand their experience with PN symptoms and any associated impacts. Interviews over the course of the trial will focus on any changes to experienced PN symptoms and impacts. A semi-structured interview guide will be provided in the separate interview study manual. These interviews will be conducted by trained independent moderators in selected countries. Participation in these interviews is optional, and subjects must indicate willingness to participate in the informed consent form. The interview results will be reported separately from the clinical study report.

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

### 8.2.1 Physical Examinations

- A full 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, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, and neurological systems.
- Targeted physical examinations are to be used by the investigator on the basis of clinical observations and symptomatology. A targeted physical examination will include, at a

minimum, assessments of the general appearance, respiratory and cardiovascular systems, skin and abdomen (liver and spleen).

Physical examination, as well as assessment of height and weight, will be performed at timepoints 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 8.3.5 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.

### 8.2.2 Height and Weight

Height and weight will be measured at the timepoints 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.

Height: The participants should take off shoes and heels should be placed against a wall with ankles together. Height should be measured in a standing position with a stadiometer. 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:

- Mosteller: $\sqrt{}$ (weight (kg) × height (cm) / 3600)

### 8.2.3 Vital Signs

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

Temperature, (same method to be used throughout the study), 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). The average of 3 BP readings, taken consecutively at intervals of at least one minute apart will be recorded in the eCRF.

Situations in which vital signs results should be reported as AEs are described in Section 8.3.5.

### 8.2.4 Electrocardiograms

Single 12-lead ECGs will be performed at timepoints as specified in the SoA after the participant has been resting semi-supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT interval corrected by Fridericia's formula (QTcF) intervals.

All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities in QTc interval detected require triplicate ECG results. At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained in succession, no more than 2 minutes apart. The full set of triplicates should be completed within 5 minutes.

Single ECGs should be performed at the time of significant LVEF drop 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.

Situations in which ECG results should be reported as AEs are described in Section 8.3.5.

### 8.2.5 Echocardiogram/Cardiac MRI

An ECHO or cardiac MRI scan to assess LVEF will be performed at the visits as shown in SoA. The modality of the cardiac function assessments must be consistent for a given participant (ie, if ECHO is used for the screening assessment for a given participant, then ECHO should also be used for subsequent scans for that participant). The participants should also be examined using the same machine and operator whenever possible, and quantitative measurements should be taken (ie, 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 or cardiac MRI assessment.

Participants experiencing an asymptomatic LVEF reduction or left ventricular systolic dysfunction should be managed according to the algorithm provided in Appendix H 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 a follow-up ECHO or cardiac MRI, ECG, vital signs, and weight performed after 30 days to evaluate the potential for reversibility.

An ECHO or cardiac MRI 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 or cardiac MRI 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/cardiac MRI scan performed within 4 weeks prior to study intervention discontinuation, the discontinuation visit ECHO/cardiac MRI scan is not required unless clinically indicated.

Situations in which ECHO/cardiac MRI scan results should be reported as AEs are described in Section 8.3.5.

### 8.2.6 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.

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

Other safety laboratory tests include assessment for pregnancy for women of child-bearing potential. A serum pregnancy test is required at screening, following that a urine or serum pregnancy test is acceptable. Pregnancy tests will be performed every cycle throughout the entire exposure period. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Where a pregnancy test is the only assessment for a cycle, a clinic visit is not required as the test may be performed offsite. The site should obtain the test result from the participant prior to the next onsite visit. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following laboratory variables will be measured.

**Table 8 Laboratory Safety Variables**

| Haematology/haemostasis (whole blood) | Clinical chemistry (serum or plasma) |
|---|---|
| Haemoglobin | Creatinine [a] |
| Leukocyte count | Bilirubin, total |
| Leukocyte differential count (absolute count) [b] | Alkaline phosphatase |
| Platelet count | AST |
| Absolute neutrophil count | ALT |
| Absolute lymphocyte count | Albumin |
| Total white blood cell count | Potassium |
| Total red blood cell count | Calcium, total |
| | Sodium |
| | Creatine kinase [c] |
| | Amylase |
| | Magnesium |
| **Urinalysis** [d] | Gamma-glutamyl transferase |
| Haemoglobin/Erythrocytes/Blood | Protein, total |
| Protein/Albumin | Urea /blood urea nitrogen [g] |
| Glucose | Coagulation variables (aPTT, PTT, and INR) [e] |
| | Phosphate |
| | Troponin [f] |

[a] Creatinine clearance and glomerular filtration rate to be calculated at screening and if clinically indicated.
[b] If absolute count is unavailable per site practice, % /ratio can be entered.
[c] Creatine kinase to be assessed in accordance with the schedule of activities and if unexplained muscle weakness or myalgia (muscle pain) occurs see Section 8.2.1 for additional information.
[d] Urine microscopy will be assessed if other urinalysis measurements are abnormal or if clinically indicated.
[e] Coagulation variables to be assessed at screening and if clinically indicated. If both aPTT and PTT tests are not performed per local laboratory it is acceptable to enter the results for the test which is performed and leave the other test result as blank/ not done. If INR is not available per site practice, Prothrombin time can be entered.
[f] 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 H.
[g] Urea or blood urea nitrogen based on local site practice.

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; CK MB, creatine kinase-myocardial band; INR, international normalised ratio; LLN, lower limit of normal; LVEF, left ventricular ejection fraction PTT, partial thromboplastin time.

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. 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 8.3.5.

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.

**NB.** In case a participant shows an AST **or** ALT ≥ 3× ULN together with TBL ≥ 2 × ULN please refer to Appendix E "Actions required in cases of increases in liver biochemistry and evaluation of HL", for further instructions.

### 8.2.7 Ophthalmologic Examinations

An ophthalmologic examination (best corrected visual acuity, IOP and slit-lamp 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 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 H.

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.

### 8.2.8 Other Safety Assessments

#### 8.2.8.1 ECOG Performance Status

ECOG performance status will be assessed at the times specified in the SoA based on the following:

0 Fully active; able to carry out all usual activities without restrictions.

1 Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).

2 Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of only limited self-care; confined to bed or chair more than 50% of waking hours.

4 Completely disabled; unable to carry out any self-care and totally confined to bed or chair.

5 Dead

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

## 8.3 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, recording, and reporting events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events and SAEs will be collected from the time of signature of the ICF, throughout the treatment period and until the follow-up period is completed. Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.11.

If the investigator becomes aware of an SAE with a suspected causal relationship to the study intervention 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 AstraZeneca.

### 8.3.2 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:

- AE (verbatim).
- The date when the AE started and stopped.
- The CTCAE grade and changes in CTCAE grade.
- Whether the AE is serious or not (Appendix B).
- Investigator causality rating against the study intervention(s) (yes or no).
- Action taken with regard to study intervention(s).
- 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.
- Seriousness criteria.
- 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 National Cancer Institute 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).

### 8.3.3 Causality Collection

The investigator should assess causal relationship between study intervention 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.

### 8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: “Have you had any health problems since the previous visit/you were last asked?”, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of

signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 8.3.5 Adverse Events Based on Examinations and Tests

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

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs, physical examinations, ophthalmologic examinations, ECGs and ECHO/cardiac MRI should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention 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 study intervention interruption).

If deterioration in a laboratory value/vital sign/ECG/ECHO or cardiac MRI 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 or cardiac MRI 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 PD, 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.

### 8.3.6 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 E for further instruction on cases of increases in liver biochemistry and evaluation of HL.

### 8.3.7 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 PD and not an AE. Events, which are unequivocally due to PD, should not be reported as an AE during the study.

### 8.3.8 Disease Under Study

Symptoms of the 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.

### 8.3.9 Deaths

All deaths that occur during the study intervention period, or within the protocol-defined follow-up period after the administration of the last dose of study intervention, must be reported as follows:

- An AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study intervention should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study intervention, then it should also be reported as an SAE.

Note: In Germany SAE reporting has to be done immediately without undue delay after obtaining knowledge.

### 8.3.10 Adverse Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of selumetinib safety profile and require close monitoring and rapid communication by the investigators to AstraZeneca. An AESI can be serious or non-serious. All AESIs 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 8.3.12. Adverse events of special interest based on examinations and tests should be reported in accordance

with Section 8.3.5. Adverse events of special interest are shown in Table 9.

**Table 9 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. |

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

### 8.3.11 Safety Data to be Collected Following the Final DCO of the Study

For participants continuing to receive selumetinib after the final DCO, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that investigators monitor the participant's safety laboratory results periodically during treatment with selumetinib in order to manage AEs, consistent with the dose modification guidelines for management of study intervention-related toxicities (see Section 6.6). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving selumetinib (or within the 30 days following the last dose of selumetinib after the final DCO must be reported as detailed in Section 8.3.12.

### 8.3.12 Reporting of Serious Adverse Events

All SAEs have to 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, then investigators or other site personnel inform the appropriate AstraZeneca representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

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

**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 is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it. Note: In Germany SAE reporting has to be done immediately without undue delay after obtaining knowledge.

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 IB for selumetinib.

### 8.3.13 Pregnancy

All pregnancies and outcomes of pregnancy with conception dates following the first date of study intervention, including pregnancy in the partner of male participants, should be reported to AstraZeneca.

#### 8.3.13.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, selumetinib should be discontinued immediately.

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

If any pregnancy occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day, ie, 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 SAEs (see Section 8.3.12) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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

#### 8.3.13.2 Paternal Exposure

Non-sterilised male participants who intend to be sexually active with a female partner of childbearing potential should refrain from fathering a child or donating or banking sperm for the duration of the study (from the time of screening) and for 7 days after the last dose of study intervention.

Pregnancy of the participant's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) occurring from the date of the first dose of study intervention until 7 days after the last dose of study intervention should be followed up and documented in the medical record and provided to the AstraZeneca Patient Safety data entry site. Consent from the partner must be obtained before the information is collected and reported to AstraZeneca.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the participant's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant Regulatory Authority/IRBs/IECs prior to use.

### 8.3.14 Medication Error, Drug Abuse, and Drug Misuse

#### 8.3.14.1 Timelines

If a medication error, drug abuse, **or** drug misuse occurs in the course of the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within 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 8.3.12) and **within 30 days** for all other events.

Note: In Germany SAE reporting has to be done immediately without undue delay after obtaining knowledge.

#### 8.3.14.2 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.

#### 8.3.14.3 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.

#### 8.3.14.4 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.

### 8.3.15 Medical Device Deficiencies

This section is not applicable.

## 8.4 Overdose

Use of selumetinib in doses exceeding that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of selumetinib and possible symptoms of overdose are not established.

- 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 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 8.3.12) and **within 30 days** for all other overdoses.

Note: In Germany SAE reporting has to be done immediately without undue delay after obtaining knowledge.

## 8.5 Human Biological Samples

Instructions for the collection, handling, storage and shipping 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.

- Remaining unused PK samples may be used for exploratory biomarker analysis as indicated in Section 8.6.2 and is subject to agreement in the ICF.
  - Samples will be stored for a maximum of 15 years from the date of the issue of the clinical study report in line with consent and local requirements, after which they will be destroyed/repatriated.
  - Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymised, individual or pooled samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the clinical study report.
  - Samples collected in China will be stored and disposed of according to local laws and regulations. PK samples collected in China will be destroyed after finalisation of Bioanalytical Report or completion of clinical study report.

For further details on Handling of Human Biological Samples, see Appendix C.

### 8.5.1 Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of selumetinib and N-desmethyl selumetinib as specified in the SoA.
- Samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and AstraZeneca, eg, 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 selumetinib. Samples collected for analyses of 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 by a bioanalytical laboratory. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

**Collection of Samples**

Blood samples will be collected for measurement of selumetinib and N-desmethyl selumetinib as shown in Table 10. The selumetinib dose dates and times must be recorded accurately on the day preceding the PK sample day and on the PK sample day.

**Table 10 Pharmacokinetic Sampling Schedule**

| | Pre-Dose [a] | 0.5 hour [b] | 1.5 hour [b] | 3 hour [b] | 6 hour [b] | 8 hour [c] |
|---|---|---|---|---|---|---|
| Cycle 1 Day 8 (Day 4 to Day 14) [d] | X | X | X | X | X | X |

[a] Within 10 minutes prior to dosing.
[b] Time allowance ± 10 minutes.
[c] Time allowance ± 15 minutes. The second dose of selumetinib should be taken after the 8 hour sample
[d] Pharmacokinetic sampling is targeted for Day 8, however for operational reasons the PK sampling can take place on any day between Day 4 and Day 14 as long as the participant has received 3 consecutive days of dosing immediately prior to the PK day. Every effort should be made to conduct PK sampling within the Day 4 – Day 14 window. However, if for unforeseen reasons this is not possible, PK sampling can be performed at any day prior to the end of Cycle 12 provided the participant has received 3 consecutive days of dosing immediately prior to the PK day.

PK, pharmacokinetics.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or 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.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

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.

Samples from participants assigned to placebo will only be analysed if there is cause to expect incorrect study drug administration.

### 8.5.2 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

## 8.6 Human Biological Sample Biomarkers

### 8.6.1 Collection of Mandatory Samples for Biomarker Analysis

Mandatory biomarker samples will not be collected in this study.

### 8.6.2 Other Study-related Biomarker Research

- Already collected PK samples may be analysed to explore potential biomarkers, which may influence the progression of neurofibromatosis and inoperable plexiform neurofibromas (and associated clinical characteristics) and/or identify participants likely to respond to selumetinib, or may be surrogate markers of response. Exploratory biomarker analysis may include (but is not limited to) pERK, cytokines, and/or quantification of RNA expression using quantitative RT-PCR, microarray or other technology in blood, PBMCs, serum, or plasma to evaluate their association with observed responses to selumetinib.
- Other study-related biomarker research excludes genomic analysis, but targeted sequence analysis on genes involved in neurofibromatosis might be included.

## 8.7 Optional Genomics Initiative Sample

Collection of optional samples for genomics initiative research is also part of this study as specified in the SoA and is subject to agreement in the ICF addendum.

Blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study. See Appendix D for information regarding the storage and destruction of genomics initiative genetic sample. Details on processes for collection and shipment and destruction of these samples can be found either in the appendices or in the Laboratory Manual.

Note: This sample will not be collected in China and will only be collected in other countries where locally applicable/permissible.

## 8.8 Medical Resource Utilisation and Health Economics

Health Economics/Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive SAP will be prepared 90 days post FSI with final amendments completed prior to DBL for DCO1.

The SAP will be signed off before review of any potential treatment-revealing data is undertaken (this includes blinded delivery reviews). For all situations, a full draft of the SAP should be available to ensure sufficient time to prepare for any blinded or unblinded data review.

## 9.1 Statistical Hypotheses

The hypothesis of interest with regards to the primary efficacy endpoint is:

- $H_0$: $ORR_{selumetinib} = ORR_{placebo}$
- $H_1$: $ORR_{selumetinib} \neq ORR_{placebo}$

Where ORR is assessed by landmark end of Cycle 16.

The hypothesis of interest with regards to the 1st key secondary endpoint is:

- $H_0$: $\mu_{Pain,\ selumetinib} - \mu_{Pain,\ placebo} = 0$
- $H_1$: $\mu_{Pain,\ selumetinib} - \mu_{Pain,\ placebo} \neq 0$

Where $\mu_{Pain}$ represents the mean change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12.

The hypothesis of interest with regards to the 2nd key secondary endpoint is:

- $H_0$: $\mu_{QoL,\ selumetinib} - \mu_{QoL,\ placebo} = 0$
- $H_1$: $\mu_{QoL,\ selumetinib} - \mu_{QoL,\ placebo} \neq 0$

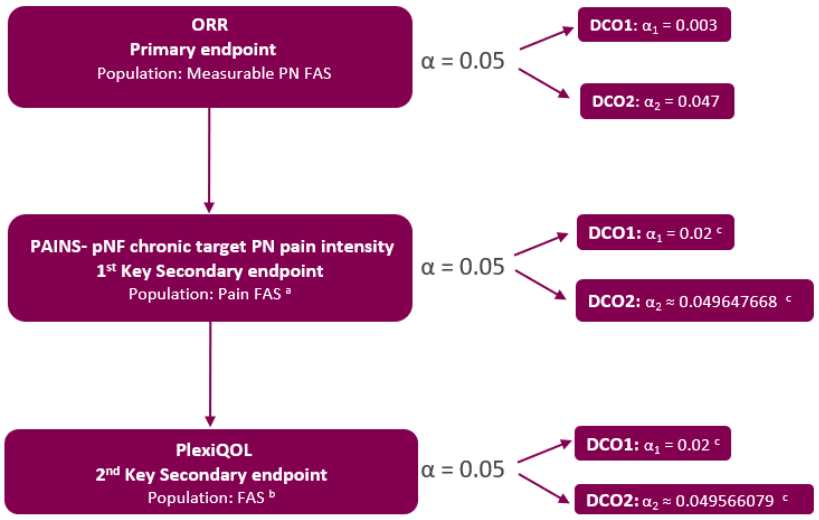
Where $\mu_{QoL}$ represents the mean change from baseline in PlexiQOL total score at Cycle 12.

The MTP will define which significance levels should be applied to the interpretation of the raw p-values for the primary endpoint (ORR by end of Cycle 16), the 1st key secondary endpoint (change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12) and the 2nd key secondary endpoint (change from baseline in PlexiQOL total score at Cycle 12) intended for label claims as described in Figure 3 and will be further detailed in the SAP.

To preserve the overall type 1 error (familywise error rate) at 5% (two-sided) in the strong

sense, the MTP will be implemented for each endpoint in order at the interim analysis (DCO1, if performed) and if required at the primary analysis (DCO2).

**Figure 3 Multiple Testing Procedure**




[a] Includes Pain FAS patients who have at least one post-baseline average cycle PAIN-pNF chronic target PN pain intensity score.

[b] Includes FAS patients who have a baseline PlexiQOL total score and at least one post-baseline PlexiQOL total score.

[c] Significance levels assuming 95.2% and 94.8% information fraction at DCO1 for 1st and 2nd key secondary endpoints, respectively. Final $\alpha_2$ will be determined at DCO1 based on the actual information fraction using the Haybittle-Peto procedure in EAST. With 100% information fraction at DCO1, $\alpha_1 = 0.05$.

DCO, data cut off; FAS, Full analysis set; $H_0$, null hypothesis; ORR, Objective response rate; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PlexiQOL, Plexiform Neurofibroma Quality of Life scale; PN, plexiform neurofibromas.

Significance levels will be adjusted for each confirmatory endpoint in order to preserve the overall type 1 error (familywise error rate) at 5% (two-sided) in the strong sense by defining a gatekeeping strategy where the families of hypotheses are tested in a sequential manner. Each family will be defined by one endpoint and the two associated tests (DCO1 and DCO2): first family based on the primary endpoint, second family based on the 1st key secondary endpoint and the third family based on the 2nd key secondary endpoint. All alpha 0.05 (two-sided) will be initially assigned to the primary endpoint. If statistical significance for the primary endpoint is reached (either at DCO1 or at DCO2), the overall alpha 0.05 (two-sided) will be sequentially re-assigned to test the 1st key secondary endpoint. If statistical significance is reached for the 1st key secondary endpoint, then the overall alpha 0.05 (two-sided) will be sequentially re-assigned to test the 2nd key secondary endpoint. If statistically significance is not reached for the primary endpoint, the p-value of the key secondary endpoints will be only nominal. If statistically significance is not reached for the 1st key secondary endpoint either at DCO1 or at DCO2, the p-value of the 2nd key secondary endpoint will be only nominal.
The interim analysis (i.e., when the 100th randomised patient has had the opportunity to have

their end of cycle 16 assessment) will take place with approximately 68.5% of the primary endpoint information expected at the primary analysis. For the first family, a split alpha strategy will be conducted where an alpha of 0.003 (two-sided) will be initially allocated to test at DCO1. If statistical significance is not reached at DCO1, the primary endpoint will be tested again at DCO2 with the remaining alpha of 0.047 (two-sided). If statistical significance of the primary endpoint is reached at DCO1 or DCO2, the overall alpha of 0.05 (two-sided) will be allocated to the 1st key secondary endpoint. Similarly, if statistical significance of the 1st key secondary endpoint is reached at DCO1 or DCO2, the overall alpha of 0.05 (two-sided) will be allocated to the 2nd key secondary endpoint. For the second and third families, the Haybittle-Peto approach will be applied within the family.

For the 2nd family, the expected information fraction (IF) at DCO1 is 95.2% and an alpha of 0.02 (two-sided) will be allocated to the DCO1 test (if statistical significance of the primary endpoint is reached at DCO1) and an alpha of 0.049647668 (two-sided) will be assigned to DCO2, if non-statistical significance is reached DCO1 and test needs to be repeated at DCO2.

Similarly for the 3rd family, the IF at DCO1 is expected to be 94.8% and an alpha of 0.02 (two-sided) will be allocated to the DCO1 test (if statistical significance of the 1$^{st}$ key secondary endpoint is reached at DCO1) and an alpha of 0.049566079 (two-sided) will be assigned to DCO2, if non-statistical significance is reached DCO1 and test needs to be repeated at DCO2.

The actual IF for each key secondary endpoint will be calculated at the time of the analysis and adjustments to the alpha will be made accordingly. If the IF is observed to be 100% at DCO1, then the overall alpha of 0.05 (two-sided) will be available for DCO1.

Testing of 1$^{st}$ key secondary endpoint will proceed as follows according to the below two scenarios regarding significance on the primary endpoint:

1. If the Primary endpoint is not statistically significant at DCO1, then the key secondary variables are not tested at DCO1. If the primary endpoint is statistically significant at DCO2, then the 1$^{st}$ key secondary endpoint will be tested at the remaining alpha left assuming it would have been tested at 0.02 at DCO1. Thus, if the IF is 95.2% at DCO1, it will be tested at 0.049647668 (two-sided) at DCO2. If the IF is higher than 95.2%, then the test at DCO2 will be conducted at a higher alpha calculated using Haybittle-Peto approach. If the IF is 100%, it will be then tested at 0.05 (two-sided).

2. If the primary endpoint is statistically significant at DCO1, then the 1$^{st}$ Key secondary endpoint will be tested at 0.02. If the IF at DCO1 is 100% then it will be tested at 0.05.

The same approach will be applied to the testing of the 2$^{nd}$ key secondary endpoint based on the significance of the 1$^{st}$ key secondary endpoint, using their corresponding IF and alpha

levels.

## 9.2 Sample Size Determination

Approximately 212 participants will be enrolled to achieve approximately 146 participants randomly assigned to study intervention.

Randomisation will be stratified by average baseline PAINS-pNF chronic target PN pain score and geographical region. The number of participants randomised will be capped at approximately 106 participants with an average baseline PAINS-pNF chronic target PN pain score ≥ 3 and approximately 40 participants with an average baseline PAINS-pNF chronic target PN pain score < 3.

| | |
|---|---|
| Enrolled | Estimated 212 participants |
| Randomly assigned | Selumetinib: Estimated 73 participants<br>Placebo: Estimated 73 participants |

Note: “Enrolled” means a participant’s 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 are not randomly assigned in the study, are considered ”screen failures”, unless otherwise specified by the protocol.

With a sample size of 73 participants per arm, a Fisher’s Exact Test with a two-sided alpha of 5% will have >99% power to detect the difference between selumetinib ORR of 20% and placebo ORR of 0%. The ORR of 20% in the selumetinib arm by end of Cycle 16 is assumed from ad hoc modelling performed using the SPRINT NCI and ICR data and the Adult NF1 NCI study response rates. The ORR of 0% in the placebo arm is assumed because at the end of Cycle 16, participants randomised to placebo will only have received 4 cycles of selumetinib post-crossover, therefore any response detected post-crossover at end of Cycle 12 will be unconfirmed. Spontaneous shrinkage ≥20% during the first 12 cycles of placebo treatment is also not expected (Akshintala et al 2020).

Forty-two participants per arm are required for the study to have 90% power to detect a treatment difference of ≥ -2 in the 1st key secondary endpoint change from baseline of PAINS-pNF chronic target PN pain score (assuming an SD of 2.8) in favour of selumetinib compared with placebo at a two-sided alpha level of 5%. To allow for approximately 20% drop out (ie, participants without at least one postbaseline average cycle PAINS-pNF chronic target PN pain score), 106 participants with a baseline PAINS-pNF chronic target PN pain score of ≥ 3 will be randomised in a 1:1 selumetinib: placebo allocation. There is no formal sample size calculation regarding randomising 40 participants with baseline PAINS-pNF chronic target PN pain score of < 3; however, this is deemed sufficient to ensure the target population of adults

with NF1 and symptomatic, inoperable PN (including those with little or no baseline PN pain) are represented.

By assuming a 20% drop out (i.e, participants without at least one post baseline PlexiQoL total score), 58 participants per arm will provide at least 80% power to detect a treatment difference at Cycle 12 in the 2nd key secondary endpoint change from baseline of PlexiQoL total score (assuming an SD of 2.3) of at least -1.2 in favour of selumetinib compared with placebo at a two-sided alpha level of 5%. Refer to Table 11. to some scenarios for the statistical power for the 2nd key secondary endpoint with different mean difference in the change from baseline of the PlexiQoL total score at Cycle 12 between the two treatment groups. This range of possible treatment effects for selumetinib that could be observed in a multinational population was extrapolated based on the differences observed in other HRQoL scores in other rare disease studies as compared to an Adult selumetinib cohort (Study D1346C00011).

**Table 11 Scenarios for the power of the second key secondary endpoint**

| Mean Treatment Difference | Statistical Power |
|---|---|
| -0.7 | 37% |
| -0.8 | 47% |
| -0.9 | 56% |
| -1 | 65% |
| -1.1 | 73% |
| -1.2 | 80% |
| -1.3 | 86% |
| -1.4 | 91% |
| -1.5 | 94% |
| -1.6 | 96% |
| -1.7 | 98% |

If it is anticipated that 20% or more of participants (across blinded study intervention groups) withdraw prior to the end of Cycle 16, for reasons other than progression, then recruitment rates withstanding, enrolment will continue to randomise at least 50% of the total number of drop-out participants to ensure the primary endpoint is adequately powered.

## 9.3 Populations for Analyses

The following populations are defined:

**Table 12 Populations for Analysis**

| Population/analysis set | Description |
|---|---|
| Enrolled | All participants who sign the ICF. |
| FAS | All participants who are randomised to study intervention in the study. Treatment groups will be compared on the basis of randomised study intervention, regardless of the study intervention actually received. Participants who were randomised but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomised. |
| Measurable PN FAS | All participants who are randomised to study intervention in the study with measurable target PN at baseline per ICR. Treatment groups will be compared on the basis of randomised study intervention, regardless of the study intervention actually received. Participants who were randomised but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomised. |
| Pain FAS | All participants with a baseline PAINS-pNF chronic target PN pain intensity score ≥ 3. Treatment groups will be compared on the basis of randomised study intervention, regardless of the intervention actually received. Participants who were randomised but did not subsequently receive study intervention are included in the analysis in the treatment group to which they were randomised. |
| Selumetinib FAS | All participants who are randomised to selumetinib with measurable target PN at baseline per ICR and who have received at least one dose of selumetinib. |
| Extended selumetinib FAS | All participants who are randomised to study intervention in the study with measurable target PN at baseline per ICR and who have received at least one dose of selumetinib, ie including participants randomised to placebo who crossover to selumetinib treatment. |
| Safety analysis set | The Safety analysis set will consist of all enrolled participants who received any amount of study intervention. Safety data will be summarised according to the treatment received. |
| PK analysis set | All participants assigned to study intervention who take at least one dose of study intervention for whom any post-dose reportable PK concentration is available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses. |
| Fed measurable PN FAS | All participants who are randomised to study intervention in the study with measurable target PN at baseline per ICR, who have received at least one dose of selumetinib in fed state (i.e participant can eat at any time point in relation to each selumetinib intake without continuing to observe the fasting restriction after the end of Cycle 24) and who have at least one evaluable scan per ICR assessment in fed state at end of Cycle 30 or later. Refer to Section 5.2.1 for the definition of participant fed state. |

## 9.4 Statistical Analyses

The SAP will be finalised prior to DCO1 database lock and it 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

The below mentioned general principles will be followed:

Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, SD, median, upper and lower quartiles, minimum, and maximum. For log-transformed data it is more appropriate to present geometric mean, CV, median, minimum and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group. Overall totals will be calculated for baseline summaries only.

Detail relating to handling the potential impact of COVID-19 on analyses will be detailed in the SAP.

For safety endpoints the last observation before the first dose of study intervention will be considered the baseline measurement unless otherwise specified.

The randomised period is defined as follows:

- For participants randomised to selumetinib: date of first dose of selumetinib until one day prior to date of Cycle 13 study intervention Day 1 or date of study intervention discontinuation (whichever occurs first).
- For participants randomised to placebo: date of first dose of placebo until one day prior to the date of first selumetinib intake (post crossover) or date of study intervention discontinuation (whichever occurs first).

Full details for handling missing data and definition of other study periods will be provided in the SAP.

### 9.4.2 Efficacy

#### 9.4.2.1 Primary Endpoint

##### 9.4.2.1.1 Calculation of PN Assessment

**Independent Central Review REiNS assessment**

The ICR will first determine the tumour volume (mL) of the target PN at the pre-treatment MRI using volumetric analysis. Then follow-up scans of the same target PN will be analysed to calculate the target PN tumour volume (mL) and percentage change in target PN volume from baseline.

For each participant, the target PN tumour response (CR, confirmed CR; PR, confirmed PR; stable disease or PD) at each post-baseline scan will be programmatically derived from the percentage change in target PN volume. If a participant has had a tumour assessment that cannot be evaluated, then the participant will be assigned a target PN tumour response of NE. This will be repeated for one non-target PN (if relevant).

Further details of the derivation of target PN tumour response, non-target PN tumour response and overall response will be detailed in the SAP.

#### 9.4.2.1.2 Objective Response Rate by end of Cycle 16

The primary endpoint objective response rate is defined as the proportion of participants 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 PR (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) by end of Cycle 16 as determined by ICR per REiNS criteria.

The primary analysis will include all randomised participants with measurable target PN at baseline as determined by ICR (Measurable PN FAS). Any confirmed CR or a confirmed PR at or prior to end of Cycle 16 which occurred after a subsequent NF1-PN treatment (following study intervention discontinuation) will not be included in the numerator for the ORR calculation.

Supportive evidence of the primary endpoint of ORR by end of Cycle 16 will include:

- Changes in target PN volume (absolute and percentage change from baseline) over time in participants randomised to selumetinib and placebo. For participants randomised to placebo, these will include data prior and post selumetinib treatment initiation.

Full details of the derivation of ORR while on-treatment and supportive derivations will be documented in the SAP

#### 9.4.2.1.3 Analysis Methods

The primary endpoint estimand is based on all randomised participants with measurable target PN at baseline per ICR (Measurable PN FAS).

Data obtained using on-treatment MRI volumetric assessments from first dose up until progression (if progression occurs prior to end of Cycle 16) or the last evaluable assessment up to and including end of Cycle 16 assessment in the absence of progression will be included in the primary endpoint assessment of ORR.

Participants who discontinue randomised treatment without progression, receive a subsequent NF1-PN therapy and then respond at or prior to end of Cycle 16 will not be included as

responders in the primary endpoint ORR by end of Cycle 16. Participants with no post-baseline MRI assessments up to and including end of Cycle 16 will be considered as non-responder (ie, not having a cCR or cPR).

Intercurrent events are addressed as follows:

- Post randomised study intervention discontinuation scans will not be included in the analysis assuming a while-on-treatment strategy to the intercurrent event of randomised study intervention discontinuation (including early crossover from placebo and progression) prior to end of cycle 16 due to any reason.
- Scans after the first 28 days of a prolonged study intervention interruption until study intervention has recommenced for at least 28 days will not be included in the analysis, assuming a while-on-treatment strategy to the intercurrent event of prolonged study intervention interruption (defined as a study intervention interruption greater than or equal to 28 days).
- Scans after target PN resection will be included in the analysis assuming a treatment policy approach to the intercurrent event of target PN resection.
- Scans after subsequent NF1-PN treatment will not be included in the analysis assuming a while-on-treatment strategy to the intercurrent event of subsequent NF1-PN treatment.

The primary endpoint ORR will be compared at the landmark end of Cycle 16 between selumetinib versus placebo using a Fisher's exact test. ORR by end of Cycle 16 in each treatment group will be presented with corresponding 2-sided exact 95% CI based on the Clopper Pearson method (Clopper and Pearson 1934). The risk difference and 95% CI based on the Miettinen-Nurminen (score) method (Miettinen and Nurminen 1985) will also be presented.

Change in target PN volume will be analysed using descriptive statistics and trajectory plots.

A supplementary analysis will be performed including all randomised participants (FAS).

Full details of the primary endpoint ORR analyses and supportive analyses will be documented in the SAP.

#### 9.4.2.2 Key Secondary Endpoints

##### 9.4.2.2.1 PAINS-pNF chronic target PN pain intensity

The key secondary estimand is the difference of the means in the change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12 between selumetinib and placebo, amongst participants with a PAINS-pNF chronic target PN pain intensity score ≥ 3 at

baseline (Pain FAS) and at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score. Intercurrent events are addressed as follows:

- Changes to participants' chronic PN pain medication will be included assuming the treatment policy strategy to the intercurrent event of changes in participant's chronic PN pain medication.

- Post randomised study intervention discontinuation PAINS-pNF scores will not be collected and will be modelled through direct likelihood techniques assuming a hypothetical strategy to the intercurrent event of randomised study intervention discontinuation prior to end of cycle 12 due to any reason.

- PAINS-pNF scores after early crossover from placebo to selumetinib in participants with documented progression on imaging (as determined by ICR per REiNS criteria) will be set to missing assuming a while-on-treatment strategy to the intercurrent event of early crossover from placebo to selumetinib.

- PAINS-pNF scores after the first 28 days of a prolonged study intervention interruption until day prior to study intervention recommencement will be set to missing assuming a while-on-treatment strategy to the intercurrent event of prolonged study intervention interruption.

- PAINS-pNF scores after a target PN resection will be included in the analysis assuming a treatment policy approach to the intercurrent event of target PN resection.

A PAINS-pNF chronic target PN pain intensity score $\geq 3$ at baseline is used to take into account ceiling effects. Participants with a PAINS-pNF chronic target PN pain intensity score $< 3$ at baseline have very little or no possibility of improvement.

The response variable for a cycle will be the average cycle PAINS-pNF chronic target PN pain score change from baseline defined as the average of the available daily PAINS-pNF chronic target PN pain scores for the 28 days up to and including the last day of the cycle minus the baseline PAINS-pNF chronic target PN pain score. The average cycle PAINS-pNF chronic target PN pain score will only be derived if the participant meets the criteria of having at least 4 daily pain scores out of 7 days for at least 3 non-overlapping 7-day periods in the 28-day cycle. Baseline PAINS-pNF chronic target PN pain score is defined as the average of the available daily PAINS-pNF chronic target PN pain scores in the screening period. During this time, participants must complete their pain diary for at least 4 days out of 7 days for at least 2 non-overlapping 7-day periods in order to determine the participant's average baseline chronic target PN pain intensity score.

**Scoring**

Each of the two items on the PAINS-pNF (usual [chronic] pain and spikes of PN pain) are treated as an individual score ranging from 0 to 10. For example, when administered daily for 7 days consecutively, this results in 7 usual (chronic) PN pain scores and 7 spikes of PN pain scores.

**Analysis Methods**

For each participant, mean change from baseline in PAINS-pNF chronic target PN pain intensity score at each cycle will be calculated using the average cycle PAINS-pNF chronic target PN pain score minus baseline PAINS-pNF chronic target PN pain score.

The difference in the mean change from baseline at Cycle 12 will be analysed for PAINS-pNF chronic target PN pain intensity using a mixed model repeated measures (MMRM) analysis. The MMRM model will include treatment, cycle number and geographical region as categorical fixed effects, the baseline PAINS-pNF chronic target PN pain intensity score as a continuous covariate and treatment-by-cycle number and baseline PAINS-pNF score-by-cycle number interactions. Parameters will be estimated with the restricted maximum likelihood (REML) approach and the Kenward-Roger approximation is used to estimate the degrees of freedom. An unstructured covariance matrix will be used to allow for unequal treatment variance and to model the correlation between different treatment measurements within the same subject. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, autoregressive and compound symmetry.

The approach to examine missingness will be described in the SAP.

In addition, supplementary analyses for alternative estimands will be detailed in the SAP, including specifying a composite strategy for the intercurrent events of study intervention discontinuation and increase in chronic PN pain medication (based on data collected in the e-Diary and investigator's assessment of pain medication as outlined in Section 8.1.8.3) such that data not collected post study intervention discontinuation and potential confounding from pain medication are addressed.

#### 9.4.2.2.2 PlexiQoL

The key secondary estimand is the difference of the means in the change from baseline in PlexiQOL total score at Cycle 12 between selumetinib and placebo, amongst FAS participants with an baseline PlexiQOL total score and at least one post-baseline PlexiQOL total score. Intercurrent events are addressed as follows:

- Post randomised study intervention discontinuation PlexiQOL scores will not be collected and will be modelled through direct likelihood techniques assuming a hypothetical strategy to the intercurrent event of randomised study intervention discontinuation prior to end of cycle 12 due to any reason.

- PlexiQOL scores after early crossover from placebo to selumetinib in participants with documented progression on imaging (as determined by ICR per REiNS criteria) will be set to missing assuming a while-on-treatment strategy to the intercurrent event of early crossover from placebo to selumetinib.

- PlexiQOL scores after the first 28 days of a prolonged study intervention interruption until day prior to study intervention recommencement will be set to missing assuming a while-on-treatment strategy to the intercurrent event of prolonged study intervention interruption.

- PlexiQOL scores after a target PN resection will be included in the analysis assuming a treatment policy approach to the intercurrent event of target PN resection.

The response variable for a specific cycle will be the PlexiQOL change from baseline defined as the PlexiQOL total score at that cycle minus the baseline PlexiQOL total score.

**Scoring**

Each statement on the PlexiQoL is given a score of 1 = True or 0 = Not true. A score of "1" is given where the item is affirmed, indicating adverse quality of life. According to the PlexiQoL user manual, it is recommended that for respondents with between one and three missing responses (that is, cases with no more than 20% missing data), the total score is calculated as follows: all item scores are summed to give a total score that ranges from 0 (good QoL) to 18 (poor QoL). This total score is then divided by the number of non-missing items and multiplied by 18. Cases with more than three missing responses cannot be allocated a total score.

Difference in change from baseline in PlexiQoL items between selumetinib and placebo will be evaluated at post-baseline cycles and overall over the randomised treatment period.

The change from baseline in PlexiQoL total score over the duration of the study will also be evaluated.

**Analysis Methods**

For each participant, change from baseline in PlexiQOL total score at the end of each cycle where PlexiQOL is measured during the randomised period (cycles 2, 4, 8 and 12) will be calculated.

The difference in the mean change from baseline at Cycle 12 will be analysed for PlexiQOL total score using a MMRM analysis. The MMRM model will include treatment, cycle number and geographical region as categorical fixed effects, the baseline PlexiQOL total score as a continuous covariate and treatment-by-cycle number and baseline PlexiQOL total score-by-cycle number interactions. Parameters will be estimated with the restricted maximum likelihood (REML) approach and the Kenward-Roger approximation is used to estimate the degrees of freedom. An unstructured covariance matrix will be used to allow for unequal treatment variance and to model the correlation between different treatment measurements within the same subject. If the fit of the unstructured covariance structure fails to converge, the following covariance structures will be used in order until convergence is reached: toeplitz with heterogeneity, autoregressive with heterogeneity, toeplitz, autoregressive and compound symmetry.

The approach to examine missingness will be described in the SAP.

In addition, supplementary analyses for alternative estimands will be detailed in the SAP,

Full details of the analysis of PlexiQoL items will be documented in the SAP.

#### 9.4.2.3 Secondary Endpoints

##### 9.4.2.3.1 Objective Response Rate (single-arm)

Objective response rate is defined as described in Section 9.4.2.1.2.

This ORR analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR and who received at least one dose of selumetinib (Selumetinib FAS), ie, single arm assessment of ORR. Data obtained while on-treatment from first selumetinib dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of ORR. Any confirmed CR or a confirmed PR which occurred after a subsequent NF1-PN treatment (following study intervention discontinuation) will not be included in the numerator for the ORR calculation (where the selumetinib FAS will be the denominator).

Supportive evidence of the ORR (single-arm) will include:

- A supplementary analysis including all participants with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Extended selumetinib FAS). In this analysis, the baseline MRI scan for participants randomised to placebo will be defined as the last MRI scan performed on placebo treatment prior to crossing over to selumetinib treatment.

- The BOR, defined as the best objective response recorded from the start of study intervention until progression or the last evaluable MRI assessment in the absence of progression, will also be summarised by category (confirmed CR, CR, confirmed PR, PR, stable disease, PD, or NE) and treatment arm.

**Analysis Methods**

ORR will be presented with corresponding two-sided exact 95% CI based on the Clopper Pearson methods (Clopper and Pearson 1934).

The BOR will be summarised with descriptive statistics for both the selumetinib FAS and the extended selumetinib FAS.

Full details of the analyses and supportive analyses will be documented in the SAP.

#### 9.4.2.3.2 Duration of Response

Duration of Response is derived using while on-treatment MRI volumetric assessments. The DoR will be defined as the time from the date of first documented response (which is subsequently confirmed) until date of documented progression as assessed by ICR per REiNS criteria or death due to any cause (ie, date of PFS event or censoring – date of first documented response + 1).

The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Selumetinib FAS) and with a confirmed CR or confirmed PR prior to study intervention discontinuation. Full details of the derivation of DoR while on-treatment, and censoring rules will be documented in the SAP.

A supplementary analysis will be performed including all participants who received at least one dose of selumetinib and with a confirmed CR or confirmed PR prior to study intervention discontinuation. In this analysis, the baseline MRI scan for participants randomised to placebo will be defined as the last MRI scan performed on placebo treatment prior to crossing over to selumetinib treatment.

**Analysis Methods**

Descriptive data will be provided for the DoR in responding participants, including the associated Kaplan-Meier curves. Full details of the DoR summaries will be documented in the SAP.

#### 9.4.2.3.3 Progression Free Survival

Progression free survival will be derived using while on-treatment MRI volumetric assessments and is defined as the time from the date of first selumetinib dose until date of

progression by ICR per REiNS criteria or death (due to any cause), ie, date of event or censoring – date of the first dose of selumetinib + 1.

Participants who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable REiNS assessment.

The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Selumetinib FAS).

A supplementary analysis will be performed including all participants with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Extended Selumetinib FAS). In this analysis, the baseline MRI scan for participants randomised to placebo will be defined as the last MRI scan performed on placebo treatment prior to crossing over to selumetinib treatment.

Full detail for the derivation of PFS while on-treatment and censoring rules will be documented in the SAP.

**Analysis Methods**

Descriptive data will be provided for PFS, including the associated Kaplan-Meier curve. Full details of PFS summaries will be documented in the SAP.

#### 9.4.2.3.4 Time to Progression

Time to progression will be derived using while on-treatment MRI volumetric assessments. Time to progression will be defined as the time from the date of first selumetinib dose until date of documented objective disease progression by ICR per REiNS criteria, ie, date of objective disease progression or censoring – date of first dose of selumetinib + 1.

The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Selumetinib FAS).

A supplementary analysis will be performed including all participants with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Extended selumetinib FAS). In this analysis, the baseline MRI scan for participants randomised to placebo will be defined as the last MRI scan performed on placebo treatment prior to crossing over to selumetinib treatment.

Full detail for the derivation of TTP, while on-treatment and censoring rules will be documented in the SAP.

**Analysis Methods**

Descriptive data will be provided for the TTP, including the associated Kaplan-Meier curves.

Full details of TTP summaries will be documented in the SAP.

#### 9.4.2.3.5 Time to Response

Time to response will be derived using while on-treatment MRI volumetric assessments and is defined as the time from date of first dose of selumetinib until the date of first documented objective response (which is subsequently confirmed), by ICR per REiNS criteria, ie, date of first documented objective response – date of first dose of selumetinib + 1.

Data obtained from the first selumetinib dose up until progression, or the last evaluable assessment in the absence of progression, will be included in the assessment of TTR.

The analysis will include all participants randomised to selumetinib with measurable target PN at baseline per ICR and who received at least one dose of selumetinib (Selumetinib FAS) and with a confirmed CR or confirmed PR prior to selumetinib discontinuation.

A supplementary analysis will be performed including all participants with measurable target PN at baseline per ICR who received at least one dose of selumetinib (Extended selumetinib FAS) and with a confirmed CR or confirmed PR prior to selumetinib discontinuation. In this analysis, the baseline MRI scan for participants randomised to placebo will be defined as the last MRI scan performed on placebo treatment prior to crossing over to selumetinib treatment.

Full details of the derivation of TTR, while on-treatment and censoring rules will be documented in the SAP.

**Analysis Methods**

Descriptive data will be provided for TTR. Full details of TTR summaries will be documented in the SAP.

#### 9.4.2.3.6 Best Percentage Change from Baseline in Target PN

The difference in the best percentage change from baseline in target PN volume by ICR per REiNS criteria between selumetinib and placebo during the randomised period will be assessed.

The best percentage change from baseline in target PN volume will be derived using while on-treatment MRI volumetric assessments during the randomised period (see definition in Section 9.4.1). The analysis will include a subset of all participants randomised to study intervention with measurable target PN at baseline per ICR (Measurable PN FAS) with at least one post-baseline target PN volume during the randomised period.

**Analysis Methods**

Full details of the best percentage change from baseline in target PN volume analysis will be documented in the SAP.

#### 9.4.2.3.7 Chronic Target PN Pain Palliation

Chronic target PN pain palliation is defined as an improvement of ≥ 2 in average cycle PAINS-pNF chronic target PN pain intensity score and no increase in chronic PN pain medication compared to baseline for that cycle. The average cycle PAINS-pNF chronic target PN pain score is defined as the average of the available daily PAINS-pNF chronic target PN pain scores for the 28 days up to and including the last day of the cycle. The average cycle PAINS-pNF chronic target PN pain score will only be derived if the participant meets the criteria of having at least 4 daily pain scores out of 7 days for at least 3 non-overlapping 7-day periods in the 28-day cycle.

A chronic target PN pain palliation responder will be identified at each cycle as participants with an average cycle PAINS-pNF chronic target PN pain score decrease from baseline ≥ 2 points who also had no increase in chronic PN pain medication use during the specific cycle based on the e-Diary (as outlined in Section 8.1.8.3). A sensitivity analysis will be performed, where no increase in pain medication use is defined based on investigator assessment.

Pain palliation will be assessed in post baseline cycles during the randomised period (see definition in Section 9.4.1) in participants in the Pain FAS.

**Analysis Methods**

The difference in the proportion of participants with chronic target PN pain palliation will be analysed at post-baseline cycles and overall over the randomised treatment period between the selumetinib and placebo arms.

Full detail of the analysis of chronic target PN pain palliation including sensitivity analyses will be documented in the SAP.

#### 9.4.2.3.8 Time to Chronic Target PN Pain Palliation

Time to chronic target PN pain palliation is defined as the time from the first dose of study drug until the cycle of chronic target PN pain palliation.

Time to chronic target PN pain palliation will be evaluated between selumetinib and placebo during the randomised period (see definition in Section 9.4.1) in participants in the Pain FAS.

Full detail for the derivation of time to chronic target PN pain palliation and censoring rules will be documented in the SAP.

**Analysis Methods**

Full details of time to chronic target PN pain palliation analysis will be documented in the SAP.

#### 9.4.2.3.9 Pain Medication

Pain medication use in each treatment group (selumetinib and placebo) at as reported using the e-Diary and as assessed by the investigator will be analysed (as described in Section 8.1.8.3) at post-baseline cycles and overall over the randomised treatment period.

Pain medication use will be assessed in evaluable participants in the FAS.

**Analysis Methods**

Full details of the analysis of pain medication use will be documented in the SAP.

#### 9.4.2.3.10 Pain Interference

**Scoring**

Responses to individual PII-pNF items are summed and divided by the number of items answered to yield a pain interference total score ranging from 0 to 6 for each assessment.

Difference in change from baseline in PII-pNF pain interference total score between selumetinib and placebo will be assessed at post-baseline cycles and overall over the randomised treatment period. The response variable is the absolute change in end of cycle PII-pNF pain interference total score from baseline.

**Analysis Methods**

The analysis population will be a subset of the FAS, including all randomised participants with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

For the analysis of PII-pNF pain interference total score over the duration of the study in participants randomised to placebo, data prior and post selumetinib treatment initiation will be provided.

A subgroup analysis will be performed by baseline PAINS-pNF chronic target PN score group. Full details of the analysis of PII-pNF pain interference total score will be documented in the SAP.

#### 9.4.2.3.11 Physical Functioning

**Scoring**

Three items selected from the PROMIS physical function item bank will be used in this study. The items capture physical function impacts separate from those related to pain interference. Raw scores are converted to a T-score.

Difference in change from baseline in PROMIS Physical Function scores between selumetinib and placebo will be assessed at post-baseline cycles and overall over the randomised treatment

period.

The change from baseline in PROMIS items over the duration of the study will also be evaluated.

**Analysis Methods**

The analysis population will be a subset of the FAS, including all randomised participants with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

For the analysis of PROMIS items over the duration of the study in participants randomised to placebo, data prior and post selumetinib treatment initiation will be provided.

A subgroup analysis will be performed by baseline PAINS-pNF chronic target PN score group. Full details of the analysis of PROMIS items will be documented in the SAP.

#### 9.4.2.3.12 PedsQL (NF1 module Acute Version 3.0-Adult Report) Skin Sensations Domain Scoring

Items are rated on a 5-point Likert scale from 0 (Never) to 4 (Almost always), and are reversed scored and linearly transformed to a 0-100 scale as follows: 0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0. Domain scores are calculated by the sum of all the items over the number of items answered.

Difference in change from baseline in the Skin Sensations domain of the PedsQL (NF1 module acute Version 3.0 – adult report) between selumetinib and placebo will be assessed at post-baseline cycles and overall over the randomised treatment period.

The change from baseline in the Skin Sensations domain of the PedsQL NF1 module acute Version 3.0 – adult report over the duration of the study will also be evaluated.

**Analysis Methods**

The analysis population will be a subset of the FAS with an evaluable baseline assessment and at least one evaluable post-baseline assessment.

For the analysis of PedsQL NF1 module – adult form Skin Sensations items over the duration of the study, in participants randomised to placebo, data prior and post selumetinib treatment initiation will be provided.

A subgroup analysis will be performed by baseline PAINS-pNF chronic target PN score group. Full details of the analysis of PedsQL NF1 module – adult form items will be documented in the SAP.

#### 9.4.2.3.13 EQ-5D-5L

**Scoring**

The EQ-5D-5L questionnaire comprises 6 questions that cover 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a VAS. For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems).

A unique EQ-5D health state, termed the EQ-5D-5L profile, is reported as a 5-digit code with a possible 3125 health states based on these responses. For example, state 11111 indicates no problems on any of the 5 dimensions. This EQ-5D-5L profile will be converted into a weighted health state utility value, termed the EQ-5D index, by applying a country-specific equation to the profile that represents the comparative value of health states. This equation is based on national 5-level valuation sets elicited from the general population, and the base case will be the UK perspective.

Respondents also assess their health today using the EQ-VAS, which ranges from 0 (worst imaginable health) to 100 (best imaginable health).

The following endpoints will be evaluated at post-baseline cycles and overall over the randomised treatment period:

- Difference in change from baseline in EQ-5D-5L score between selumetinib and placebo.
- Difference in change from baseline in EQ-VAS between selumetinib and placebo.

The change from baseline in EQ-5D-5L score and EQ-VAS over the duration of the study will also be evaluated.

**Analysis Methods**

The analysis population will be a subset of the FAS, with an evaluable baseline assessment and at least one evaluable post-baseline assessment. For the analysis of EQ-5D-5L and EQ-VAS over the duration of the study in participants randomised to placebo, data prior and post selumetinib treatment initiation will be provided.

A subgroup analysis will be performed by baseline PAINS-pNF chronic target PN score group. Full details of the analysis of EQ-5D-5L and EQ-VAS will be documented in the SAP.

#### 9.4.2.3.14 ECOG Performance Status

ECOG performance status will be summarised by visit and treatment group.

### 9.4.2.4 Exploratory Endpoints

Full details of the analysis of exploratory endpoints will be provided in the SAP.

## 9.4.3 Safety

Safety analyses will be performed based on the Safety Analysis Set. Safety data will be presented using descriptive statistics unless otherwise specified.

Baseline: In general, the baseline value for statistical analysis is the last non-missing value prior to administration of the first dose of IP. Details are described in the SAP.

### 9.4.3.1 Adverse Events

Adverse events will be coded using the most recent version of MedDRA that will have been released for execution at AstraZeneca/designee.

Adverse events will be presented for each treatment group by SOC and/or PT covering number and percentage of participants reporting at least one event and number of events where appropriate.

An overview of AEs will present for each treatment group the number and percentage of participants with any AE, AESIs, AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study treatment, as well as AEs leading to study treatment dose interruptions and AEs leading to study treatment dose reductions.

Separate AE tables will be provided that take different factors into consideration, including relationship as assessed by the investigator, maximum CTCAE grade, seriousness, death and events leading to discontinuation of study intervention as well as other action taken related to study treatment, events of special interest and other significant AEs.

An additional table will present number and percentage of participants with most common AEs. Most common (eg, frequency of $> x\%$, $\geq x\%$) will be defined in the SAP.

In accordance with the requirements of the FDA, a separate table will present non-serious AEs occurring in more than 5% of participants in any treatment group.

Key participant information will be presented for participants with AEs with outcome of death, serious AEs, and AEs leading to discontinuation of study intervention.

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

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

#### 9.4.3.2 Treatment emergent AEs

The following events are considered treatment emergent:

Adverse events with an onset date on or after first dose of IP and within 30 days after last dose of IP or up to the day prior to start of subsequent therapy, whichever comes first.

Worsening of pre-existing events on or after first dose of IP and within 30 days after last dose of IP or up to the day prior to start of subsequent therapy, whichever comes first.

Exposure-adjusted treatment emergent AEs will also be presented.

#### 9.4.3.3 Vital Signs

Vital sign parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, min, Q1, median, Q3, and max.

For each scheduled post-baseline visit, descriptive statistics for all vital sign parameters will be presented for observed values and change from baseline.

Details of vital sign analyses will be provided in the SAP.

#### 9.4.3.4 Laboratory Parameters

Laboratory parameters will be presented for each treatment group. Summary statistics for continuous variables cover n, mean, SD, min, Q1, median, Q3, and max.

For each scheduled post-baseline visit, descriptive statistics for all clinical chemistry and haematology parameters will be presented for observed values and change from baseline.

Details of laboratory analyses will be provided in the SAP.

#### 9.4.3.5 Other Safety Endpoint(s)

Other safety data, including ophthalmologic assessments, will be summarised using descriptive statistics.

### 9.4.4 Other Analyses

#### 9.4.4.1 Pharmacokinetics

Pharmacokinetic parameters will be derived for selumetinib and N-desmethyl selumetinib using plasma concentrations, including, but not limited to:

Selumetinib:

- Cmax, AUC(0-6), AUC(0-8), AUClast, CL/F, Vss/F, tmax, tlast derived after multiple dose administration.

N desmethyl selumetinib:

- Cmax, AUC(0-6), AUC(0-8), AUClast, tmax, tlast derived after multiple dose administration.
- MPAUC and MPCmax after multiple dose administration. MPAUC will be based on either AUC(0-6) or AUC(0-8) depending on which has the most reportable values.

The plasma selumetinib and N-desmethyl selumetinib concentrations and the PK parameters will be listed and presented in tabular and graphical form by analyte based on the PK Analysis Set.

Geometric mean (± geometric SD) plasma concentration versus nominal sampling time will be plotted in a linear and semi-logarithmic scale with all treatments (periods) overlaid on the same figure and with a separate plot for each analyte.

Further data presentation and reporting details will be provided in the SAP.

Details of population PK exposure response/safety analyses will be described in the modelling analysis plan finalised before database lock. The population PK exposure response/safety analyses will be presented separately from the main clinical study report.

#### 9.4.4.2 Biomarker Analysis

- Exploratory biomarkers in plasma will be summarised by scheduled sample time points and change from pre-dose and consent to sample re-used.
- 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.

#### 9.4.4.3 Optional Exploratory Genetic Sample

Data will be reported outside the clinical study report (please see Appendix D).

## 9.5 Interim Analyses

The SAP will describe the planned interim analyses in greater detail. Significance levels will

be adjusted for each endpoint in order to preserve the overall type 1 error (familywise error rate) at 5% (two-sided) in the strong sense. Endpoints included in the MTP will be tested hierarchically, therefore if the interim analysis indicates significant ORR, then the key secondary endpoints will be tested in the following order: 1) PAINS-pNF chronic target PN pain intensity score and if this endpoint has a significant p-value then 2) PlexiQOL total score. The results of these analyses may form the basis of submissions for regulatory approval.

The interim analysis (DCO1) is expected to occur when the 100$^{th}$ randomised participant has had the opportunity to complete their end of Cycle 16 assessment. This corresponds to approximately 68.5% of the primary endpoint information expected at the primary analysis (DCO2).

The overall alpha of 0.05 (two-sided) will be first assigned to the primary endpoint (ORR by end of Cycle 16), of which an alpha of 0.003 (two-sided) will be allocated at the interim analysis. If the primary endpoint is statistically significant at the interim analysis, then the overall alpha of 0.05 (two-sided) will be re-assigned to the 1$^{st}$ key secondary endpoint (mean change from baseline in PAINS-pNF chronic target PN pain intensity score at Cycle 12), and an alpha of 0.02 (two-sided) will be allocated to the 1$^{st}$ key secondary endpoint at the interim analysis. If the 1$^{st}$ key secondary endpoint is statistically significant at the interim analysis then the overall alpha of 0.05 (two-sided) will be re-assigned to 2$^{nd}$ key secondary endpoint (change from baseline in PlexiQOL total score at Cycle 12), and an alpha of 0.02 (two-sided) will be allocated to the 2$^{nd}$ key secondary endpoint at the interim analysis.

The key secondary endpoints information fractions will be determined at the point of the interim analysis:

- For the 1$^{st}$ key secondary endpoint: The number of participants with baseline PAINS-pNF chronic target PN pain intensity score ≥3 who have the opportunity to complete 12 cycles of treatment and have at least one post-baseline average cycle PAINS-pNF chronic target PN pain intensity score.
- For the 2$^{nd}$ key secondary endpoint: The number of participants with baseline PlexiQOL total score who have the opportunity to complete 12 cycles of treatment and have at least one post-baseline PlexiQOL total score.

Given that when the 100$^{th}$ randomised participant has completed Cycle 16, there will be more than 100 participants who will have completed Cycle 12, the information fraction for the key secondary endpoints is estimated to be very high at the interim analysis.

The interim analyses will be performed by a team of unblinded statisticians and programmers independent from AstraZeneca. The independent team will inform an unblinded review

committee (internal to AstraZeneca but independent from the study team) whether the study success criteria specified in Section 9.1 have been met, and if so, the unblinded review committee will review the unblinded interim analysis outputs to make the decision whether to unblind the study team or not prior to the primary analysis.

If the interim analysis DCO (DCO1) is due to take place within approximately 4 months or of the primary analysis DCO (DCO2), then the interim analysis may not be performed and only the primary analysis will be performed.

For further details on how the overall type 1 error (familywise error rate) is preserved at 5% in the strong sense refer to Section 9.1.

## 9.6 Data Monitoring Committee

Given that the randomised portion of the study is of limited duration, the participant population is not considered vulnerable, and the safety profile of selumetinib is well established, an IDMC is not deemed to be necessary.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# Appendix A Regulatory, Ethical, and Study Oversight Considerations

## A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki as amended at 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, 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 amendments to the 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 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.

**Regulatory Reporting Requirements for Serious Adverse Events**

- Prompt notification by the investigator to AstraZeneca of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- 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 suspected unexpected serious adverse reactions according to local regulatory requirements and AstraZeneca 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 a SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the [IB or state other documents] 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 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 study.
- 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.
  - AstraZeneca will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, IRB/IEC, and investigators. If EU Clinical Trials Regulation 536/2014 applies, AstraZeneca is required to enter details of serious breaches into the EMA CTIS. It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- 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 (e-mail address or telephone number) provided by AstraZeneca.

## A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 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 answer all questions regarding the study.
- Participants 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. Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study centre.
- 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.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF 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 AstraZeneca. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by AstraZeneca in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the participant in the informed consent
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The participant's samples will not be used for any purpose other than those described in the study protocol.

## A 5 Committees Structure

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

## A 6 Dissemination of Clinical Study Data

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 http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main D134BC00001 study results when they are available. The clinical study and/or summary of main D134BC00001 study results may also be available on other websites according to the regulations of the countries in which the main D134BC00001 study is conducted.

## A 7 Data Quality Assurance

- All participant data relating to the study will be recorded on the CRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory authority 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.

- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca 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 protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca GRAD Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

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

## A 9 Study and Site Start and Closure

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

The first act of recruitment is the first site open and will be the study start date.

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca'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, AstraZeneca shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) 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.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

## 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 AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a co-ordinating 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 (other than progression of the disease under evaluation) in a participant or clinical study participant administered a study intervention 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 (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the study intervention.

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 Definitions of Serious Adverse Event

An SAE is an AE occurring during any study phase (ie, 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.

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

**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 a 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 judgment 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 judgment 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 National Cancer Institute 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 re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With 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, for example, 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 errors)
- Wrong drug administered to participant (excluding IRT errors)

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

- Errors related to or resulting from IRT – 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

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

## C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a participant withdraws consent specifically to the subsequent 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. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used as per protocol.

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 participant's 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 that the participant 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 documented and study site notified.

# C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

**LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES**

IATA (**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, for example, 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, for example, 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 UN3373 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 Optional Genomics Initiative Sample

## D 1 Use/Analysis of DNA

- AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. This genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- This optional genetic research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of genetic analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on selumetinib continues but no longer than 15 years from the end of the study (as defined in the protocol) or other period as per local requirements.

## D 2 Genetic Research Plan and Procedures

**Selection of Genetic Research Population**

- All participants will be asked to participate in this genetic research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

**Inclusion Criteria**

- For inclusion in this genetic research, participants must fulfil all of the inclusion criteria described in the main body of the CSP and provide informed consent for the Genomics Initiative sampling and analyses.

**Exclusion Criteria**

- Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:
  - Previous allogeneic bone marrow transplant.
  - Transfusion of non-leukocyte depleted blood or blood component within 120 days of genetic sample collection.

- Healthy volunteers and paediatric participant samples will not be collected for the Genomics Initiative.

**Withdrawal of Consent for Genetic Research**

- Participants may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main CSP.

**Collection of Samples for Genetic Research**

- The blood sample for this genetic research will be obtained from the participants pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per participant for genetics during the study.

**Coding and Storage of DNA Samples**

- The processes adopted for the coding and storage of samples for genetic analysis are important to maintain participant confidentiality. Samples may be stored for a maximum of 15 years from the end of the study (as defined in the protocol), after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.
- An additional second code will be assigned to the sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).
- The link between the participant enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

### Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix A.

### Informed Consent

- The genetic component of this study is optional and the participant may participate in other components of the main study without participating in this genetic component. To participate in the genetic component of the study the participant must sign and date both the consent form for the main study and the addendum for the Genomics Initiative component of the study. Copies of both signed and dated consent forms must be given to the participant and the original filed at the study centre. The principal investigator(s) is responsible for ensuring that consent is given freely and that the participant understands that they may freely withdrawal from the genetic aspect of the study at any time.

### Participant Data Protection

- AstraZeneca will not provide individual genotype results to participants, any insurance company, any employer, their family members, general physician unless required to do so by law.
- Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca physician or an investigator might know a participant's identity and also have access to his or her genetic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genetic files would remain physically separate.

### Data Management

- Any genetic data generated in this study will be stored at a secure system at AstraZeneca and/or designated organisations to analyse the samples.
- AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

**Statistical Methods**

- The number of participants that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

# Appendix E Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## E 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. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the study intervention.

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.

## E 2 Definitions

**PHL**

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

**HL**

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the study intervention, can be found to explain the combination of increases, eg, elevated alkaline phosphatase indicating cholestasis, viral hepatitis, another drug.

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

## E 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:

- ALT ≥ 3 × ULN.
- AST ≥ 3 × ULN.
- TBL ≥ 2 × ULN.

**Local laboratories being used**

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 E 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

## E 4 Follow-up

### E 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.

### E 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 criterion "Important medical event" and causality assessment "yes/related" according to CSP process for SAE reporting.

- For participants that met PHL criteria prior to starting study intervention, the investigator is not required to submit a PHL SAE unless there is a significant change[#] in the participant's condition.
- The AstraZeneca 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 AstraZeneca Medical Monitor.
  - Complete the 3 Liver eCRF Modules as information becomes available.

**#A "significant" change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or 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 AstraZeneca Medical Monitor if there is any uncertainty.

## E 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 AstraZeneca 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 study intervention, 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 study intervention:

- 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 study intervention and seriousness criterion is medically important, according to CSP process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

# E 6 Laboratory Tests

## Hy's Law Lab Tests That May be Performed

| | |
|---|---|
| Additional standard chemistry and coagulation tests | GGT<br>LDH<br>Prothrombin time<br>INR |
| Viral hepatitis | IgM anti-HAV<br>IgM and IgG anti-HBc |
| | HbsAg<br>HCV DNA [a]<br>IgM and IgG anti-HCV<br>HCV RNA [a]<br>IgM anti-HEV<br>HEV RNA |
| Other viral infections | IgM & IgG anti-CMV<br>IgM & IgG anti-HSV<br>IgM & IgG anti-EBV |
| Alcoholic hepatitis | Carbohydrate-deficient transferrin [b] |
| Autoimmune hepatitis | Antinuclear antibody<br>Anti-liver/kidney microsomal antibody<br>Anti-smooth muscle antibody |
| Metabolic diseases | Alpha-1-antitrypsin<br>Ceruloplasmin<br>Iron<br>Ferritin<br>Transferrin [b]<br>Transferrin saturation |

CMV=cytomegalovirus; DNA=deoxyribonucleic acid; EBV=Epstein-Barr virus; GGT=gamma glutamyl transferase; HAV=hepatitis A virus; HBc=hepatitis B core antigen; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HEV=hepatitis E virus; HSV=herpes simplex virus; IgG=immune-globulin G; IgM=immuno-globulin M; INR=international normalised ratio; LDH=lactate dehydrogenase; RNA=ribonucleic acid.

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

[b] Carbohydrate-deficient transferrin and transferrin are not available in China. Study teams should amend this list accordingly.

# Appendix F Contraception Requirements

Contraception requirements for this study are as follows.

## F 1 Female Participants

Women not of childbearing potential are defined as those who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or who are post-menopausal.

Women will be considered post-menopausal if they have been amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all hormonal replacement therapy, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago.

Women of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a nonsterilised male partner must use at least 1 highly effective method of contraception (Table F11). They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (7 days after the last dose of study intervention).

Non-sterilised male partners of a woman of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period and until at least one week after the female participant's last dose of study intervention. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant. Female participants should refrain from breastfeeding throughout this period.

## F 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a female partner of childbearing potential must be using an acceptable method of contraception such as male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout the total duration of the study and the drug washout period (one week after the last dose of study intervention) to prevent pregnancy in a partner.

Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male participants should refrain from sperm donation or banking throughout this period.

Vasectomised (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study.

Female partners (of childbearing potential) of male participants must also use a highly effective method of contraception throughout this period (Table F11).

## F 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table F11. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

## Table F11 Highly Effective Methods of Contraception (< 1% Failure Rate)

| Non-hormonal methods | Hormonal methods |
|---|---|
| • Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant)<br>• Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia)<br>• Bilateral tubal occlusion<br>• Intrauterine device (provided coils are copperbanded) | • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) [a]<br>• Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]<br>• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®)<br>• Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®)<br>• Combined pill: Normal and low dose combined oral contraceptive pill<br>• Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®)<br>• Mini pill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill |

[a] Hormonal methods not prone to drug-drug interactions.

# Appendix G Patient-reported Outcomes

## G 1 PAINS-pNF

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## G 2 PII-pNF

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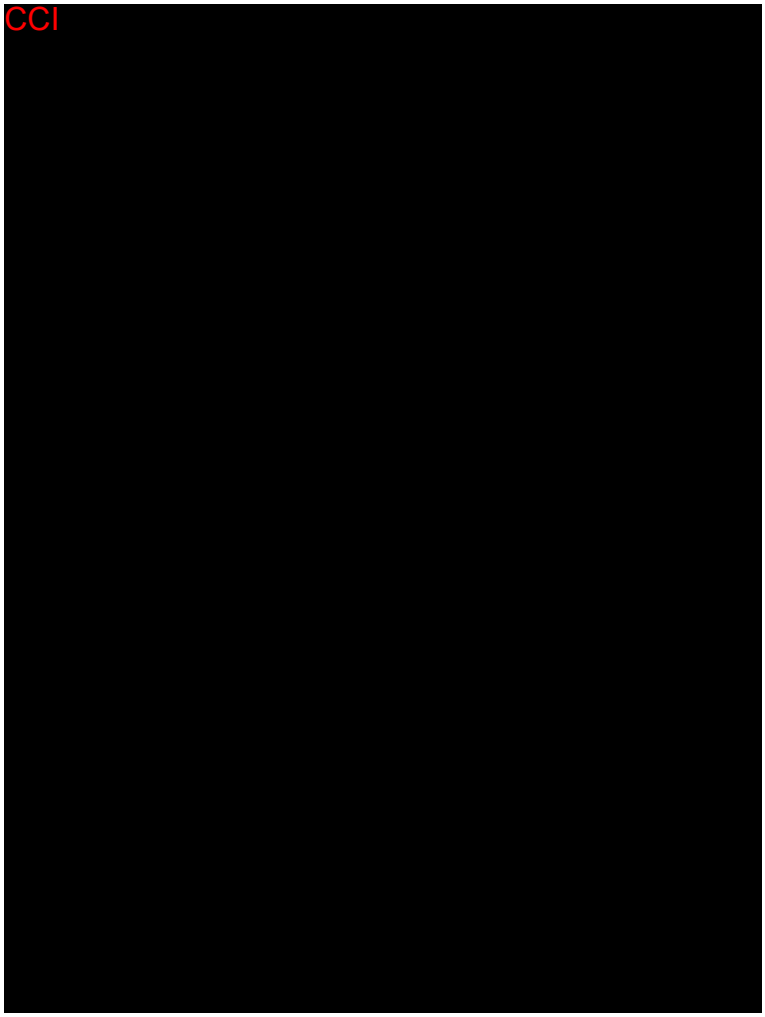

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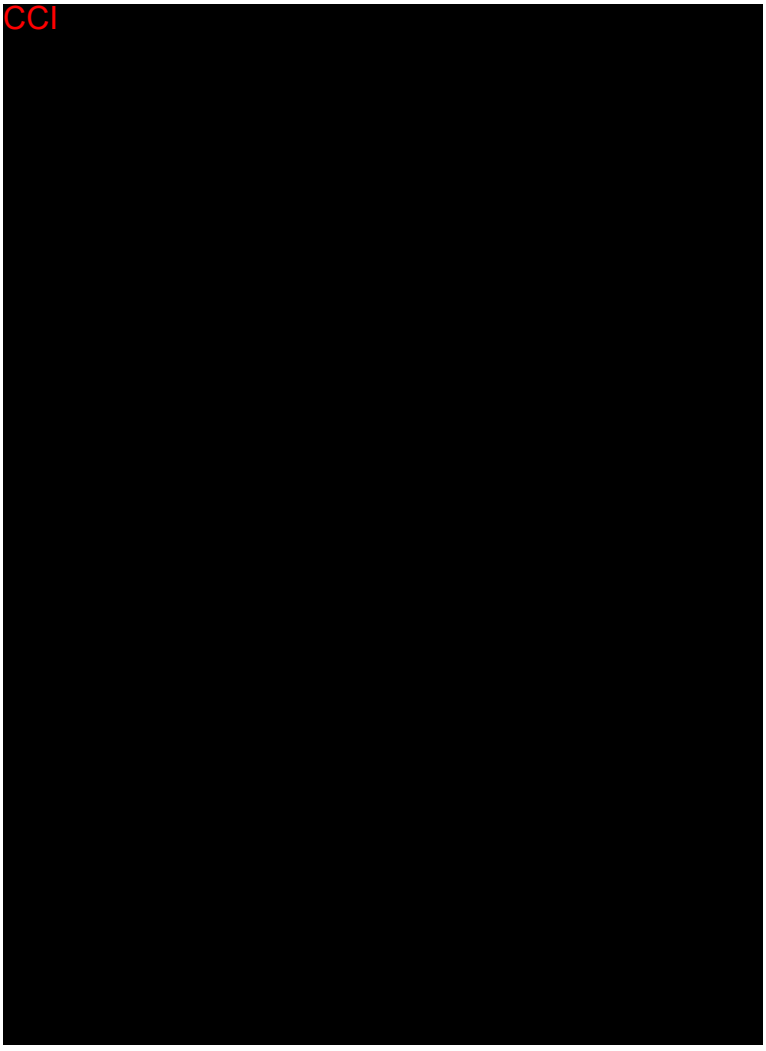

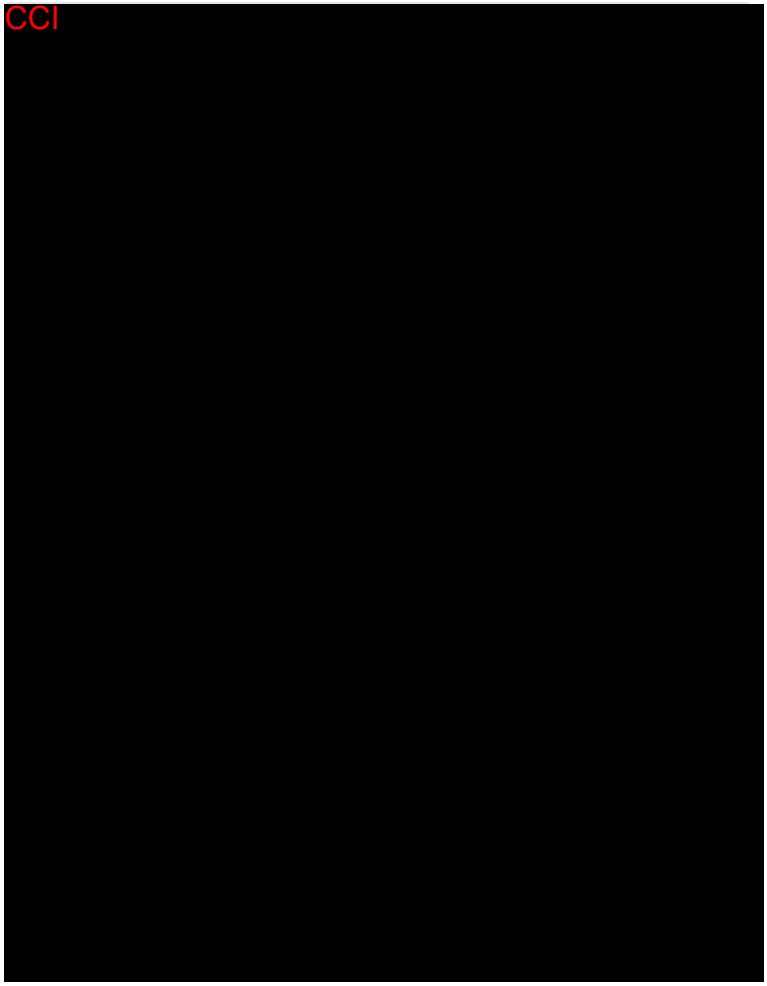
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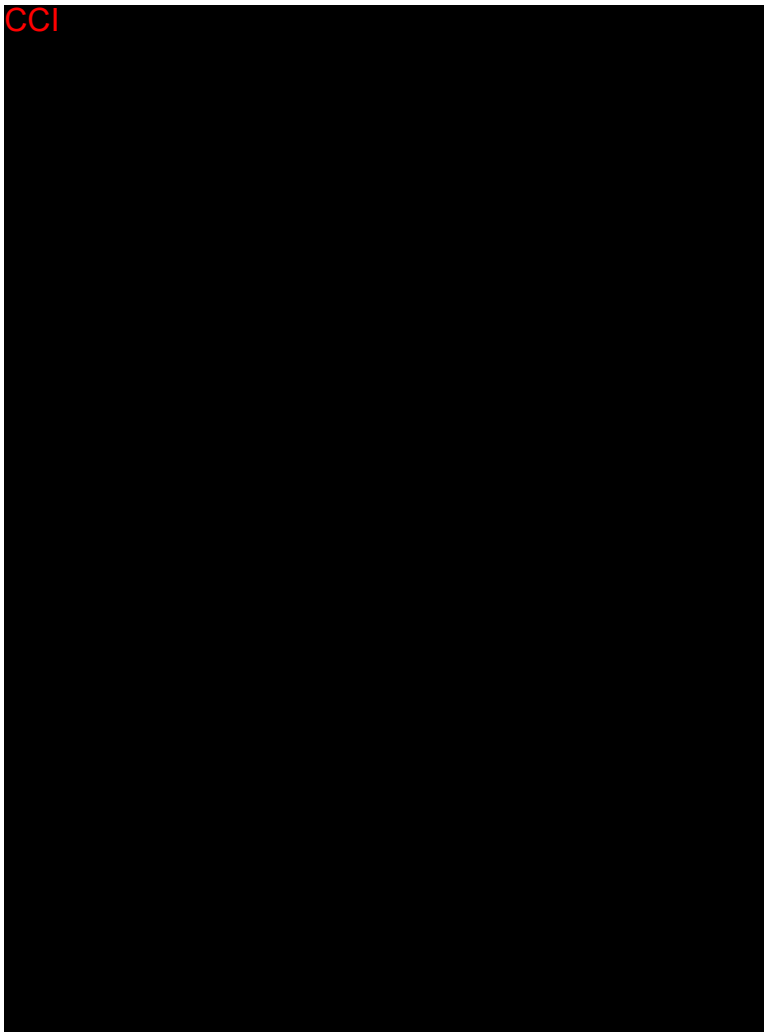
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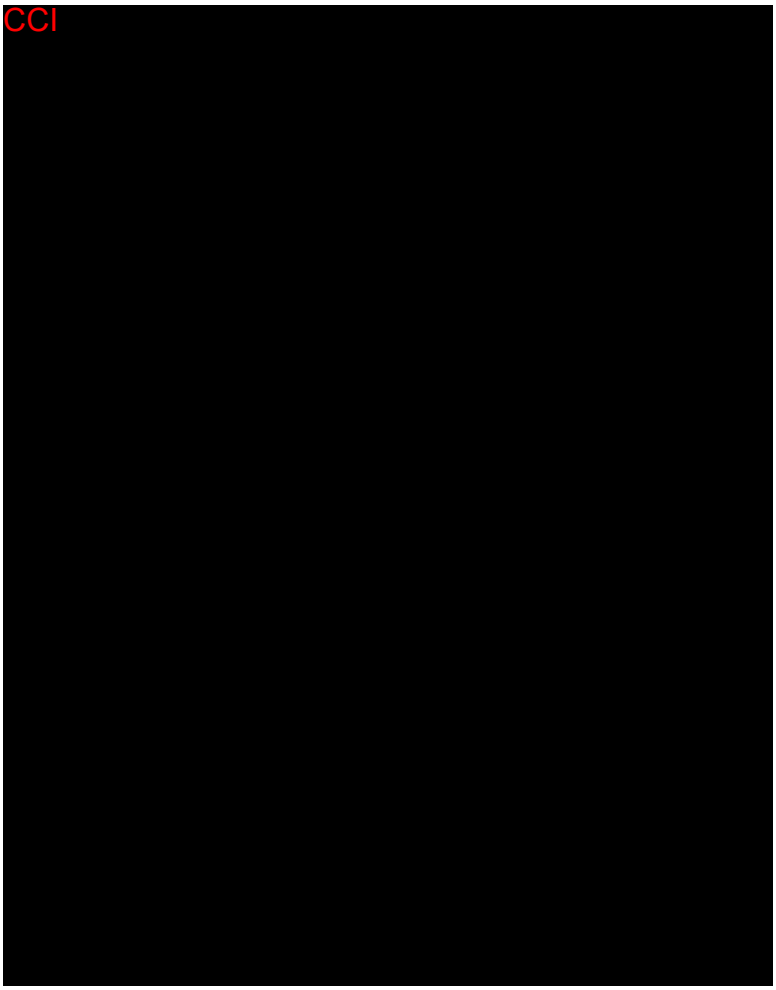
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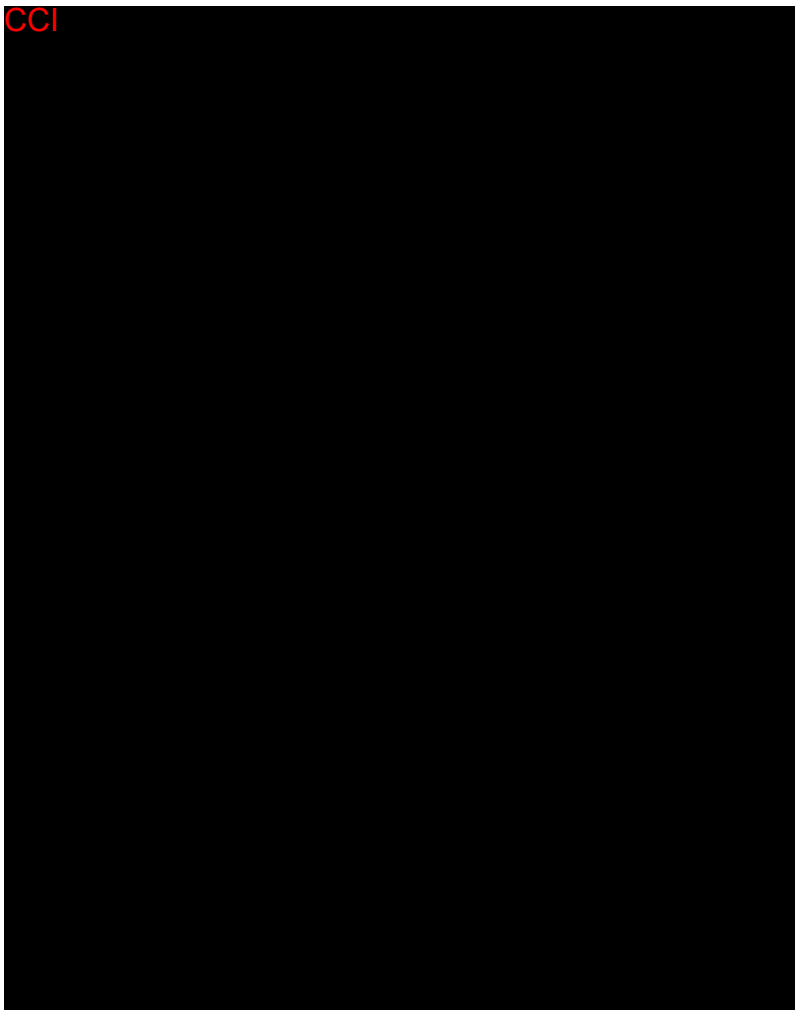
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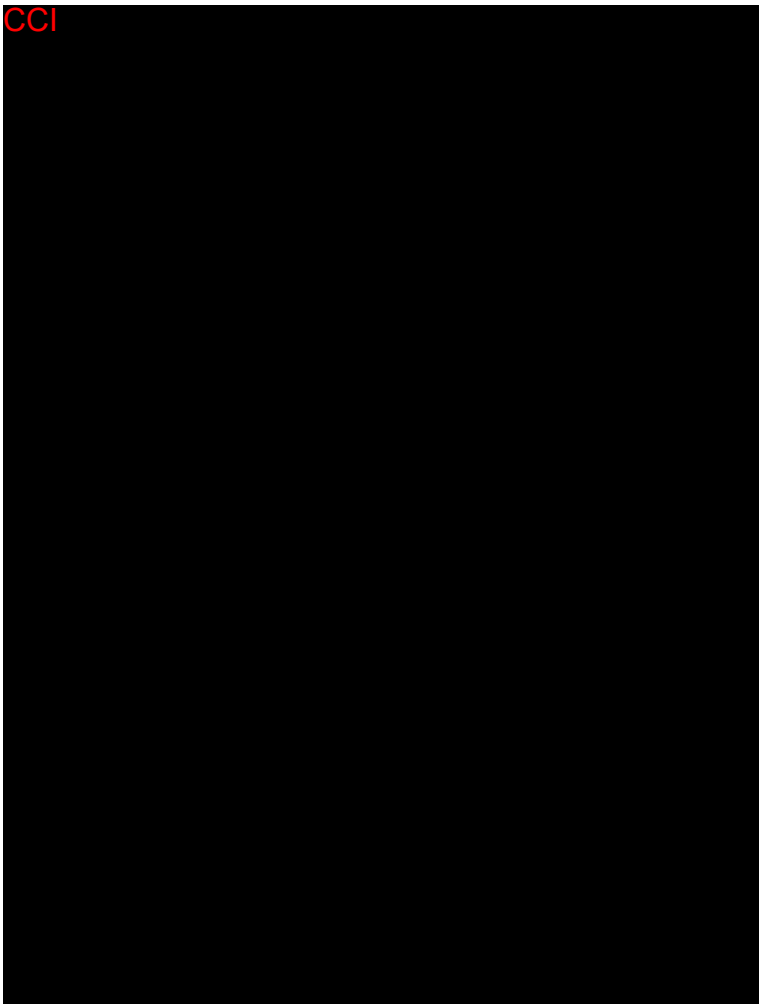
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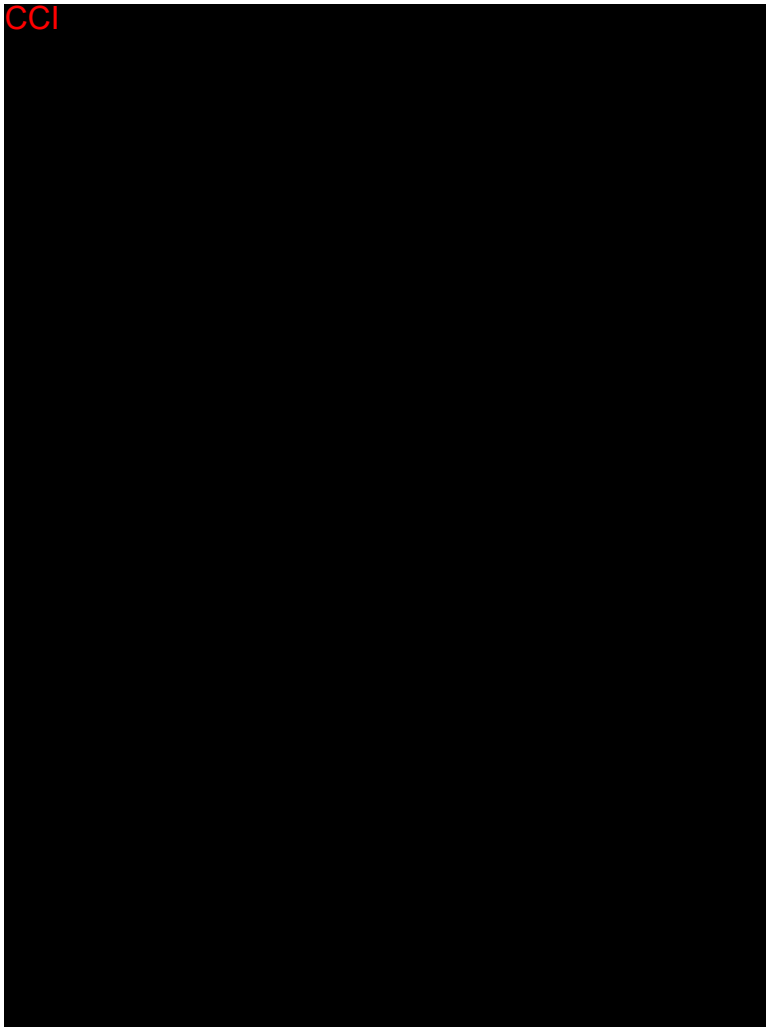
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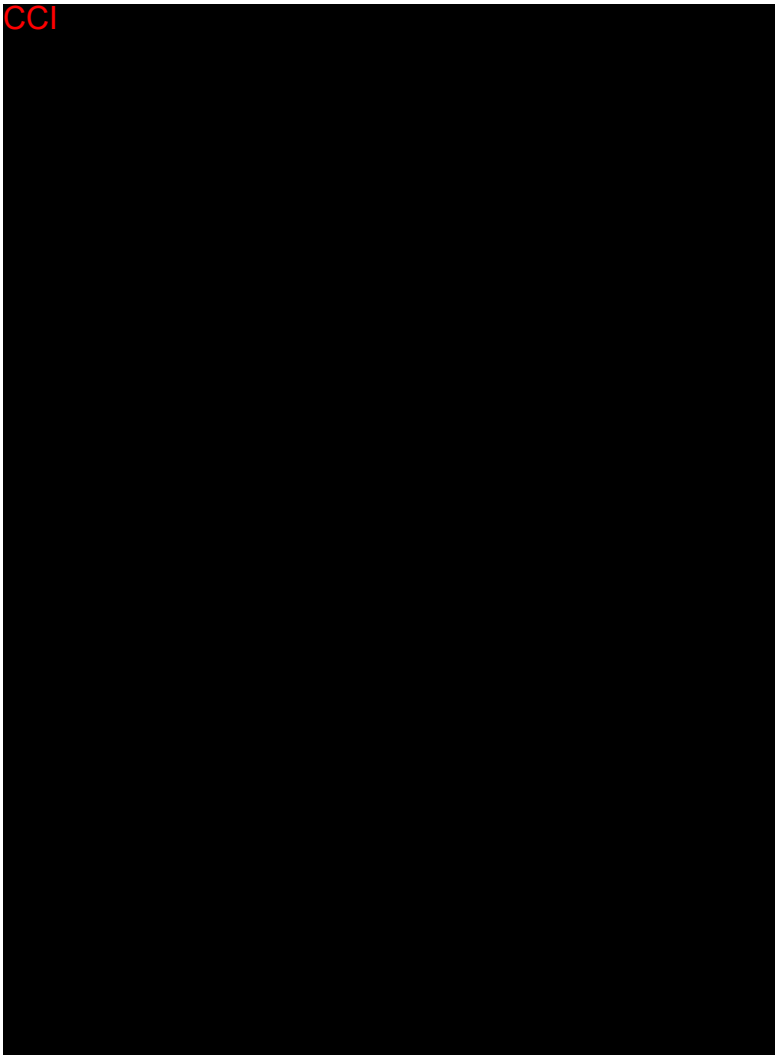
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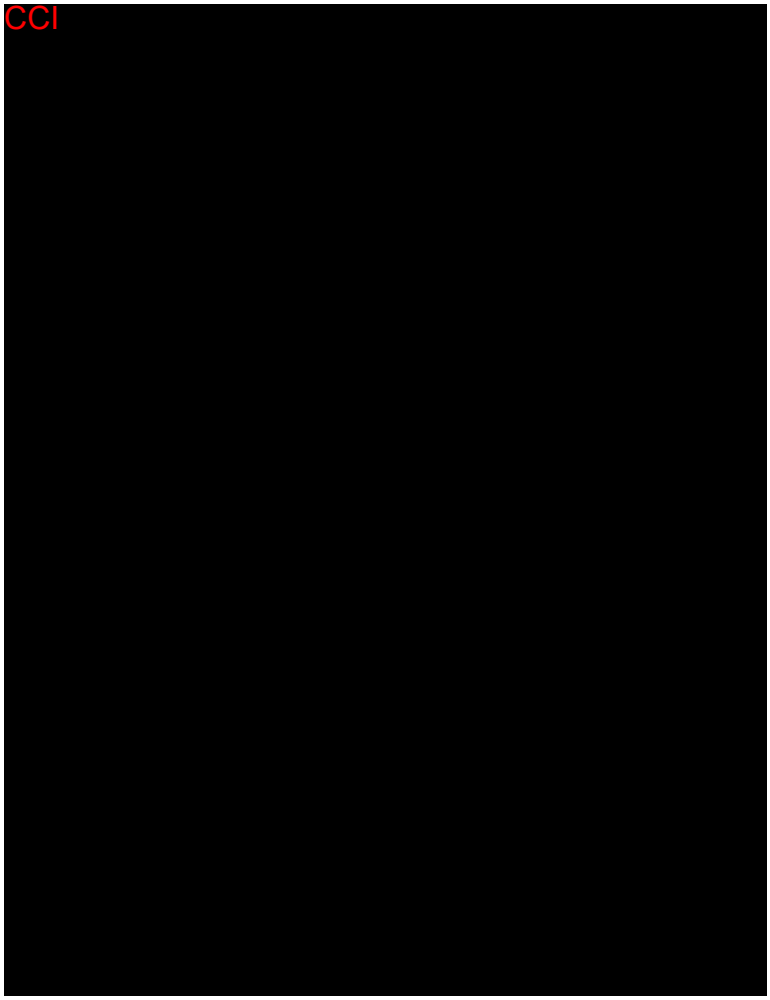
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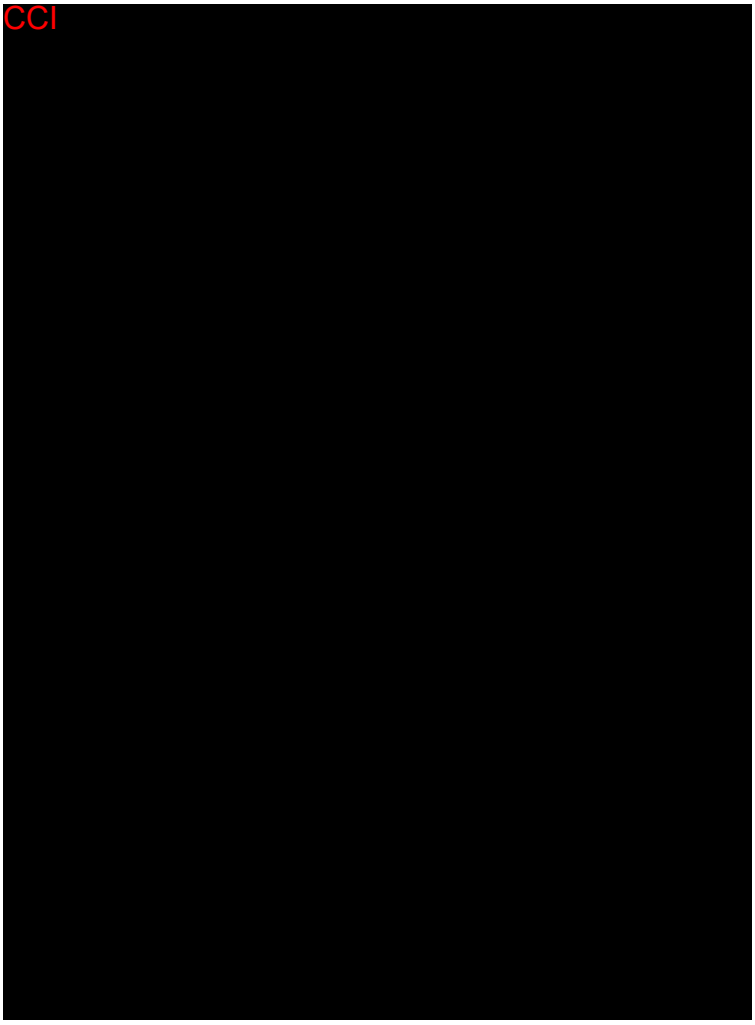

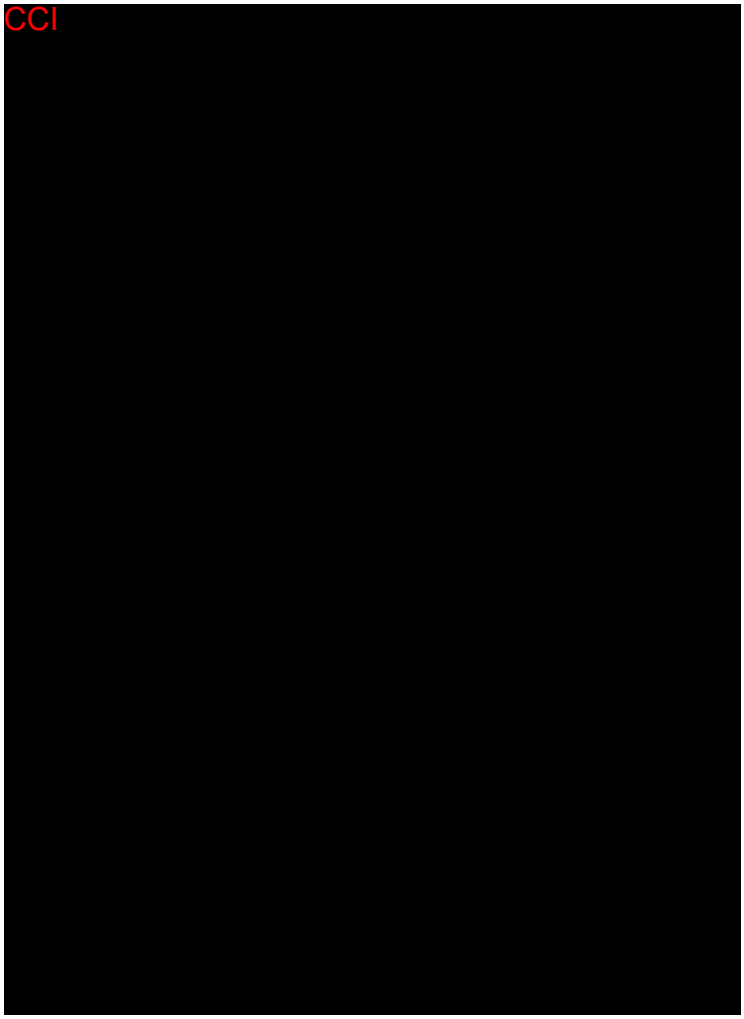
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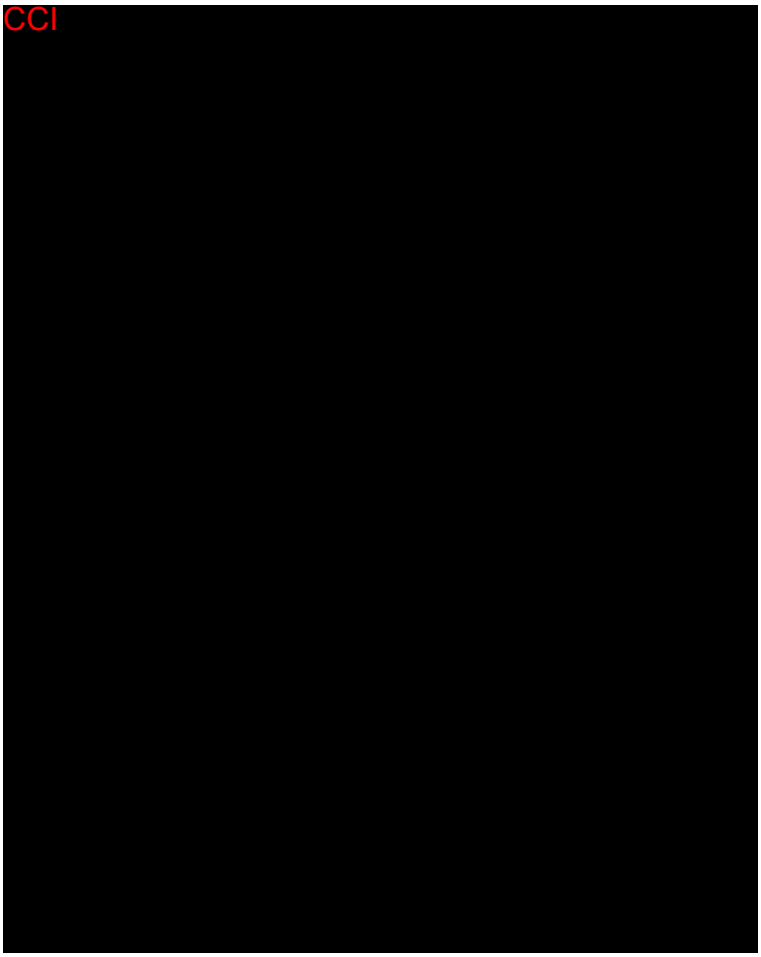
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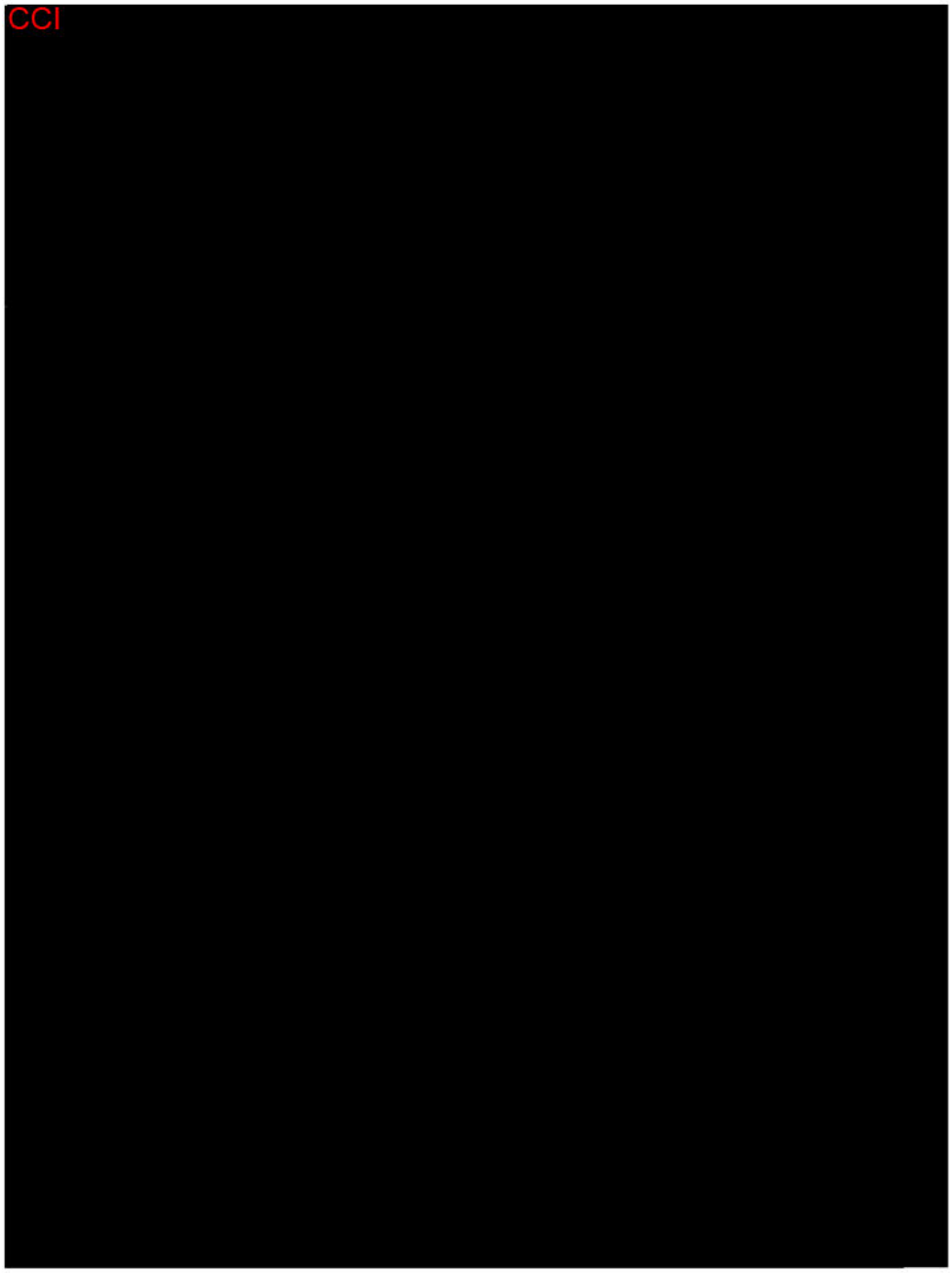
## G 3 PROMIS

# G 4 PlexiQoL



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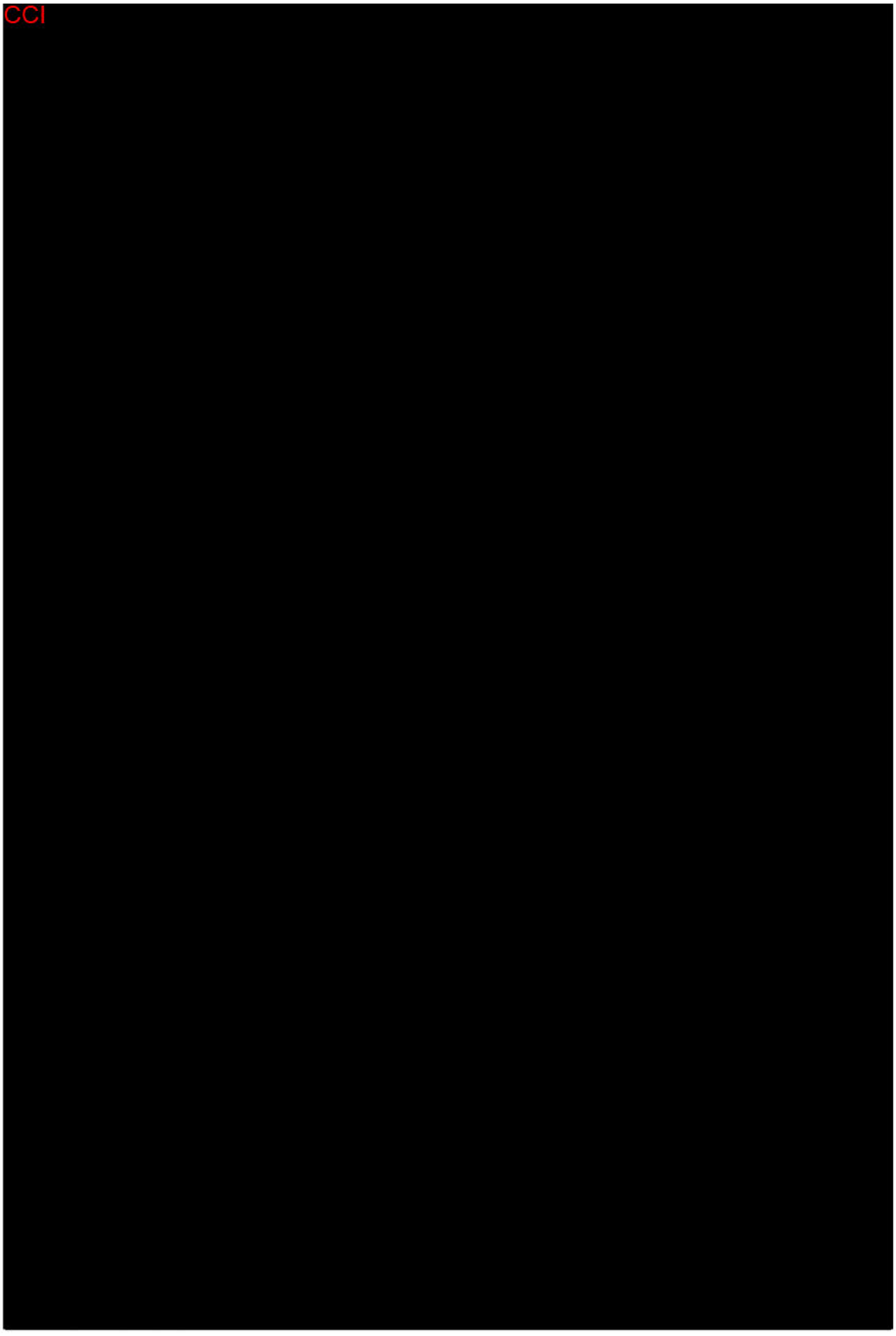
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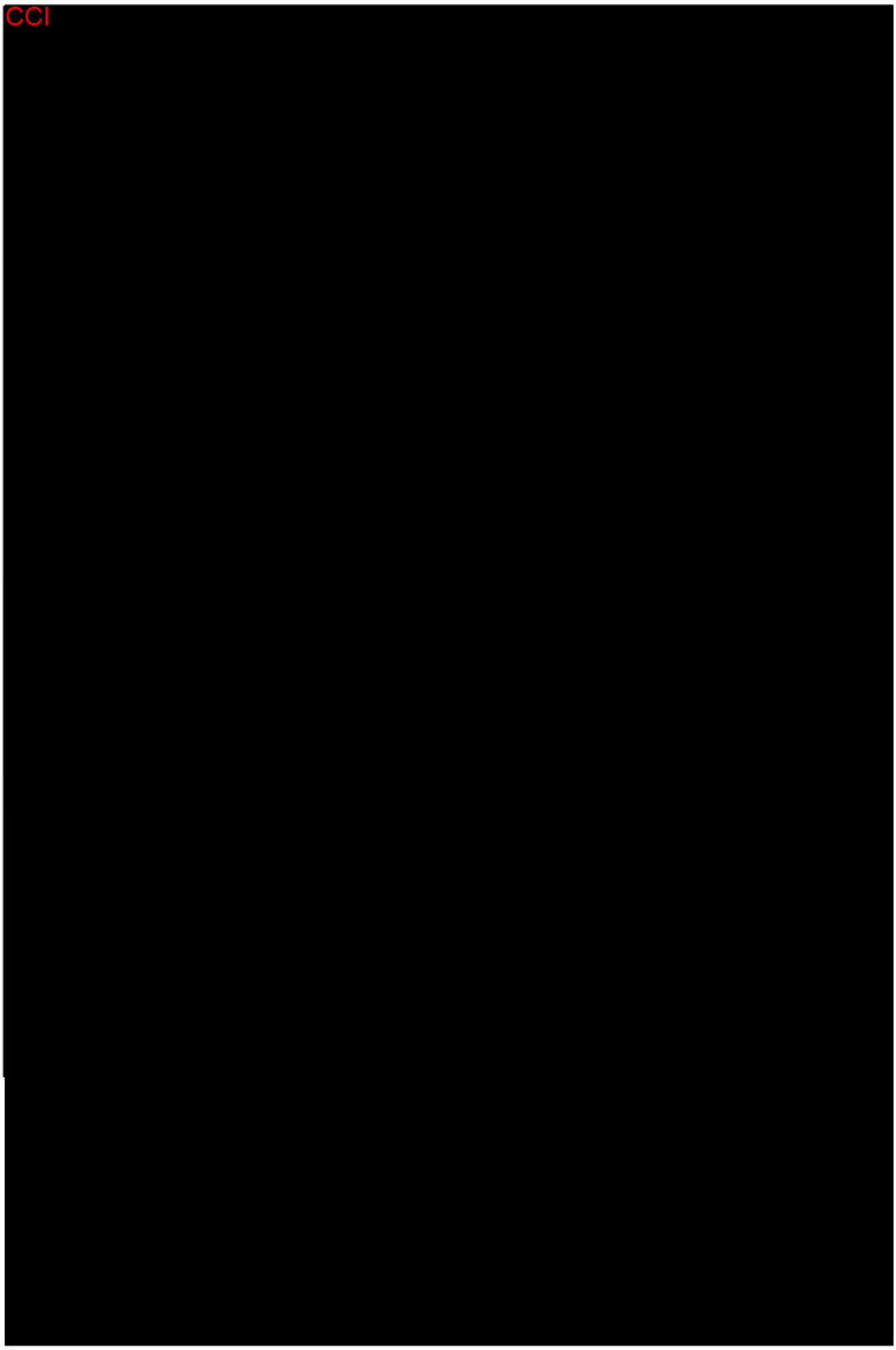


## G 5 PedsQL NF1 Module Acute Version 3.0-Adult Report (Skin Sensations Domain)

CCI

## G 6 PGIC

***Patient Global Impression Of Change (1)***

Overall, how would you rate the change in your plexiform neurofibroma related chronic pain **since your last visit to the study site**?

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same/No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

Overall, how would you rate the change in your plexiform neurofibroma related spikes of pain **since your last visit to the study site**?

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

### *Patient Global Impression Of Change (2)*

Overall, how would you rate the change in your plexiform neurofibroma related chronic **pain since starting the study medication**?

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same/No change
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

Overall, how would you rate the change in your plexiform neurofibroma related spikes of pain **since starting the study medication**?

- ☐ Much better
- ☐ Moderately better
- ☐ A little better
- ☐ About the same
- ☐ A little worse
- ☐ Moderately worse
- ☐ Much worse

# G 7 PGIS

## *Patient Global Impression Of Severity*

You have answered daily diary questions about a plexiform neurofibroma tumour that was selected by your doctor. Please think about **this area of your body** when answering the following questions.

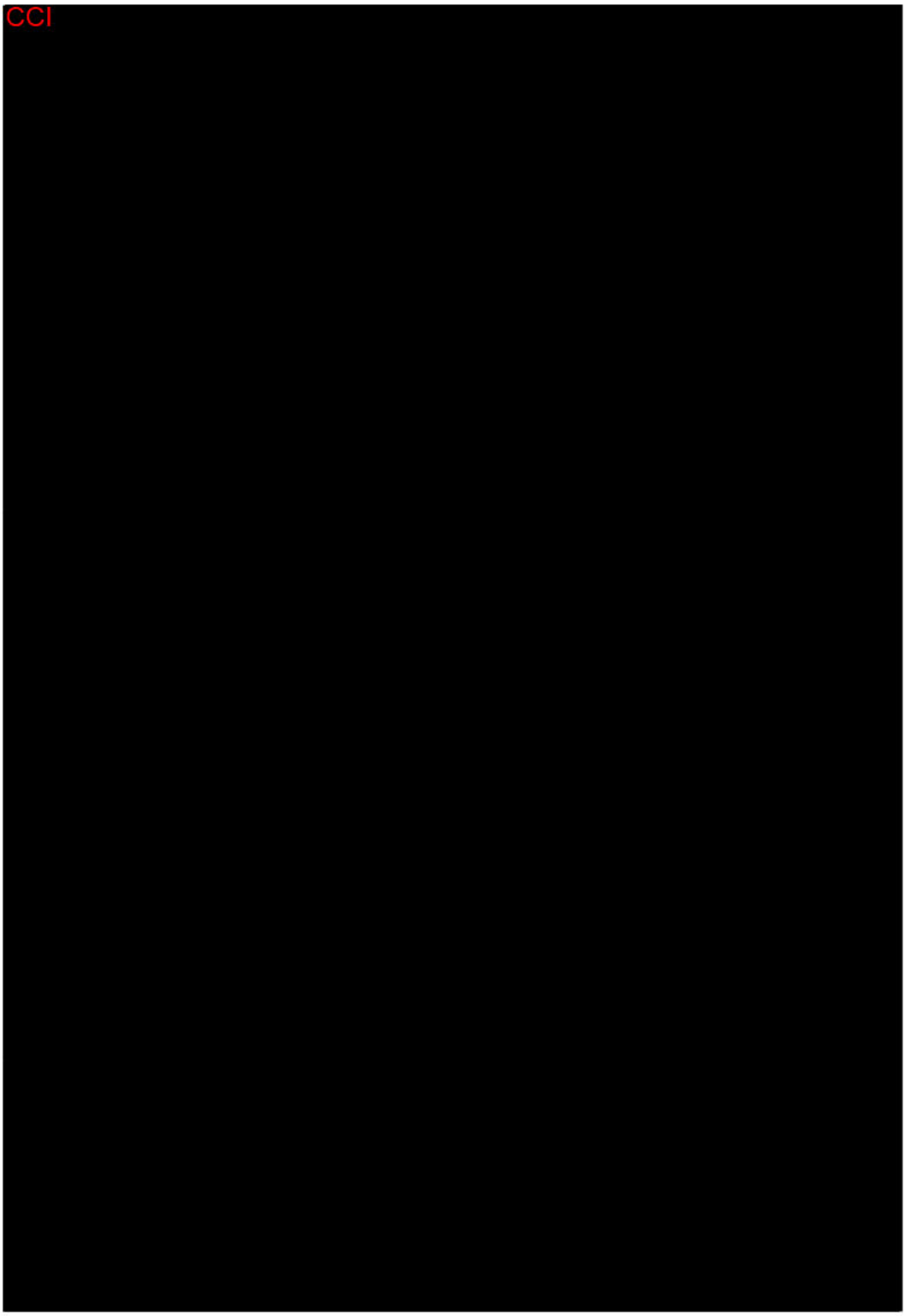
Please select the response below that best describes the severity of your plexiform neurofibroma-related chronic pain over the past 7 days.

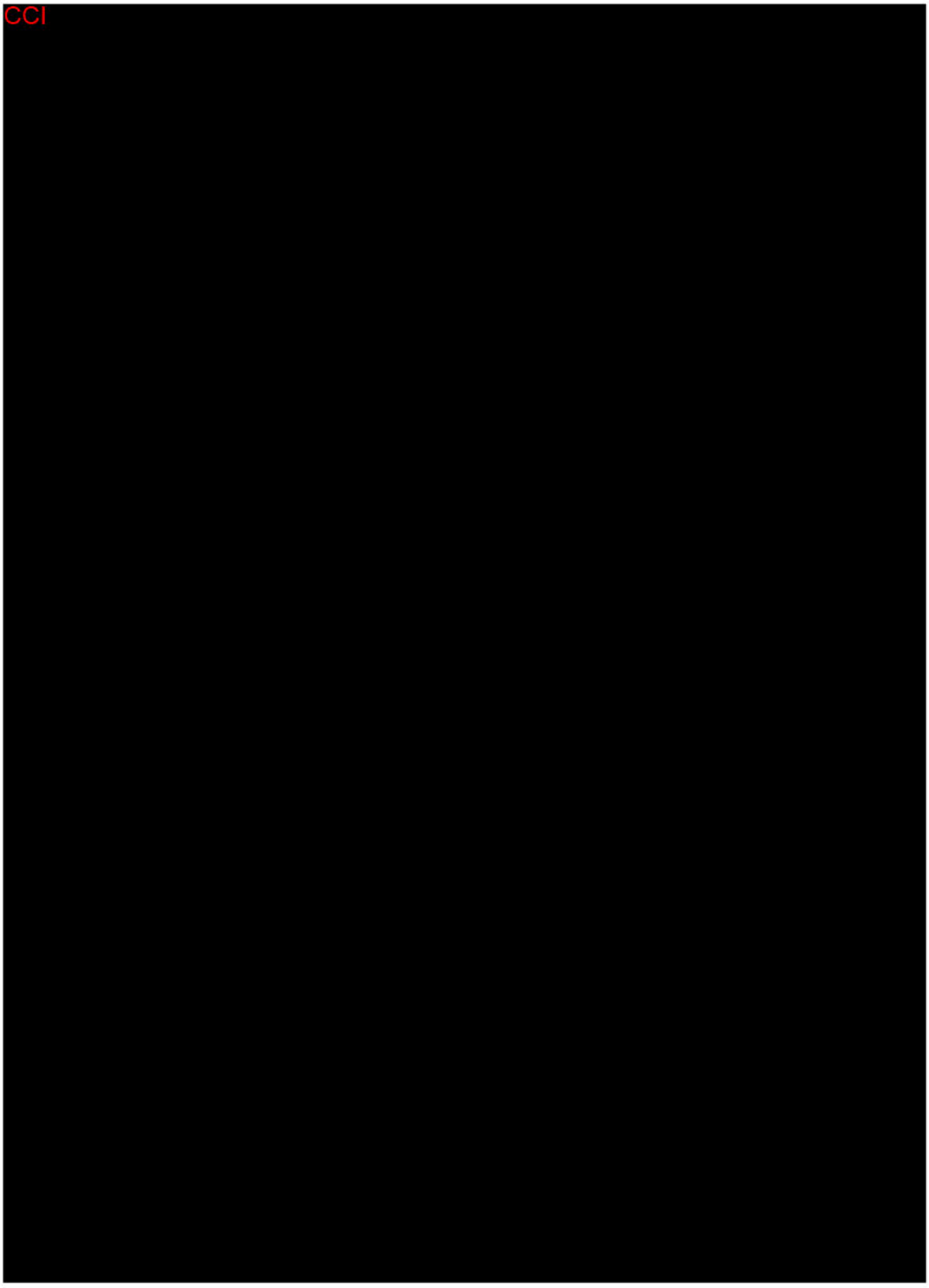
- ☐ No pain
- ☐ Mild
- ☐ Moderate
- ☐ Severe

Please select the response below that best describes the severity of your plexiform neurofibroma related spikes of pain over the past 7 days.

- ☐ No pain
- ☐ Mild
- ☐ Moderate
- ☐ Severe

# G 8 EQ-5D-5L Health Questionnaire

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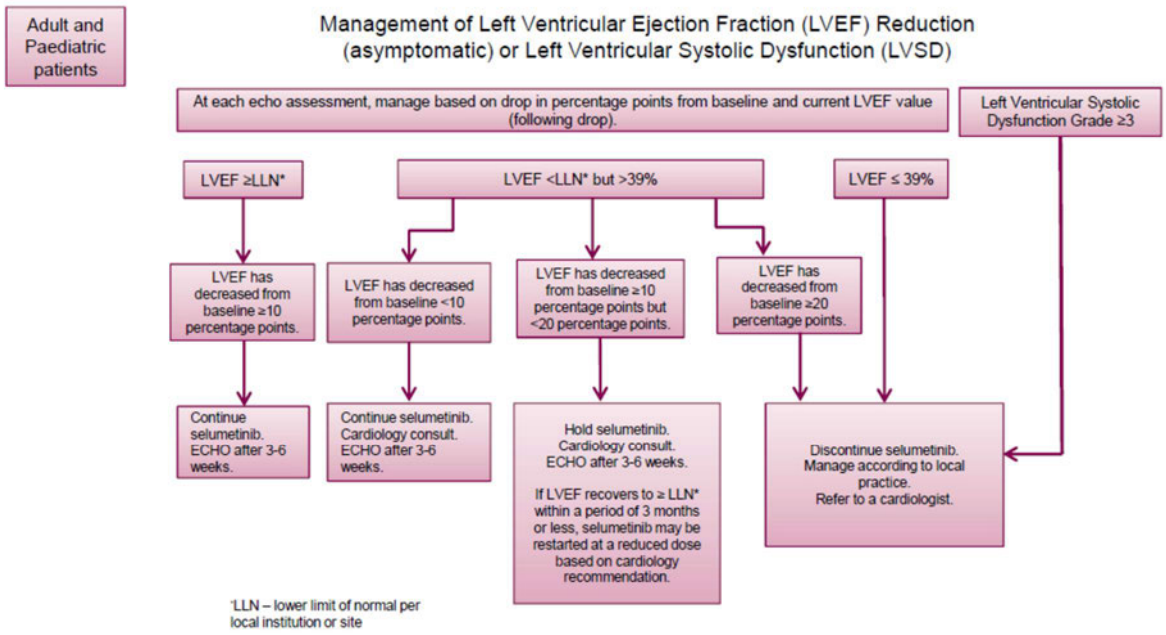
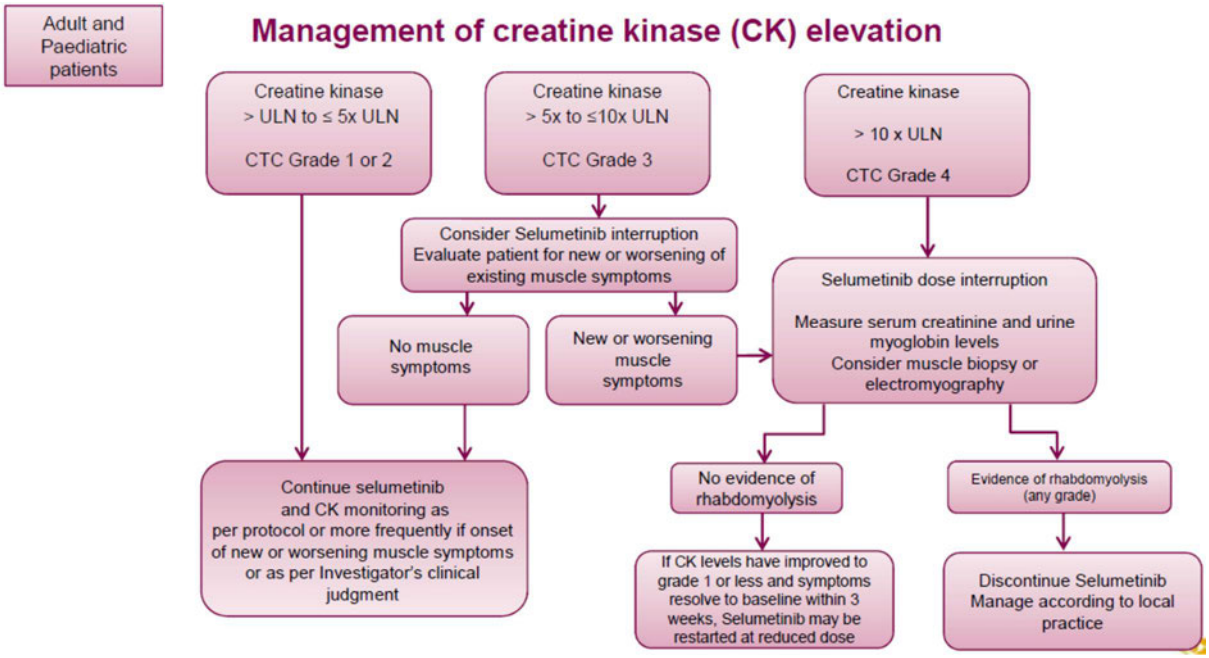
# Appendix H Guidance for Management of Specific Adverse Events

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



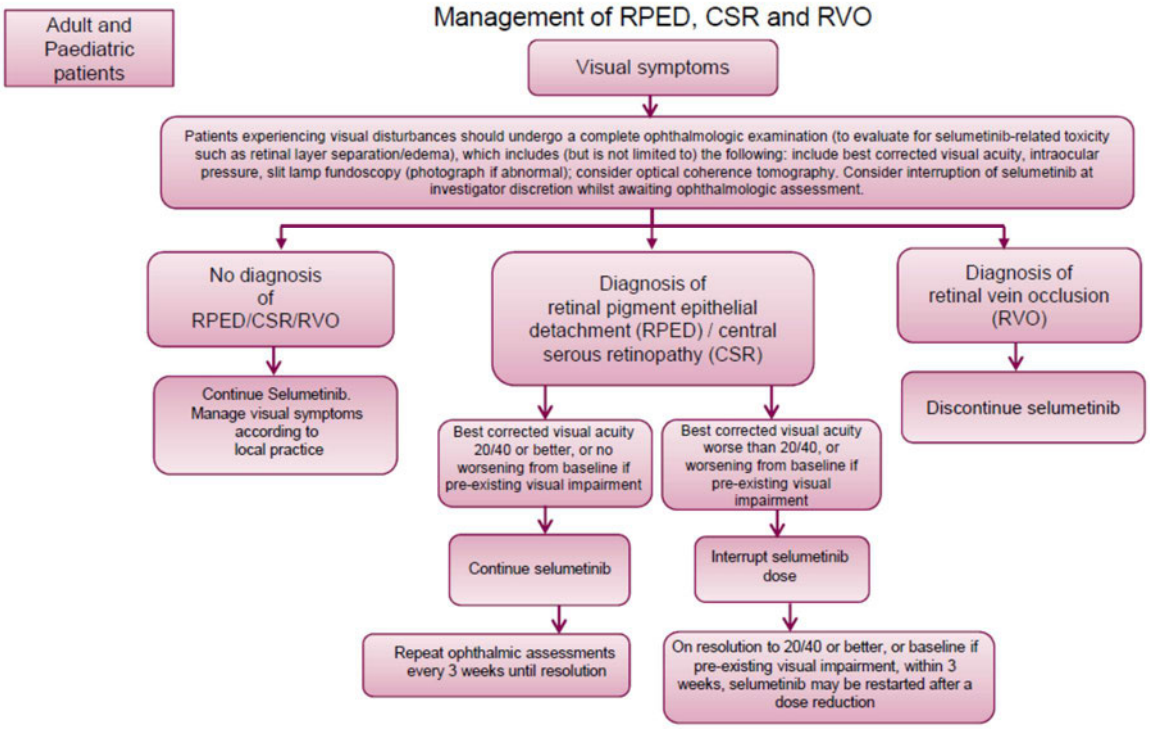

ECHO, echocardiogram; LLN, lower limit of normal, LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction.

## H 2 Management of Creatine Kinase (CK) Elevation



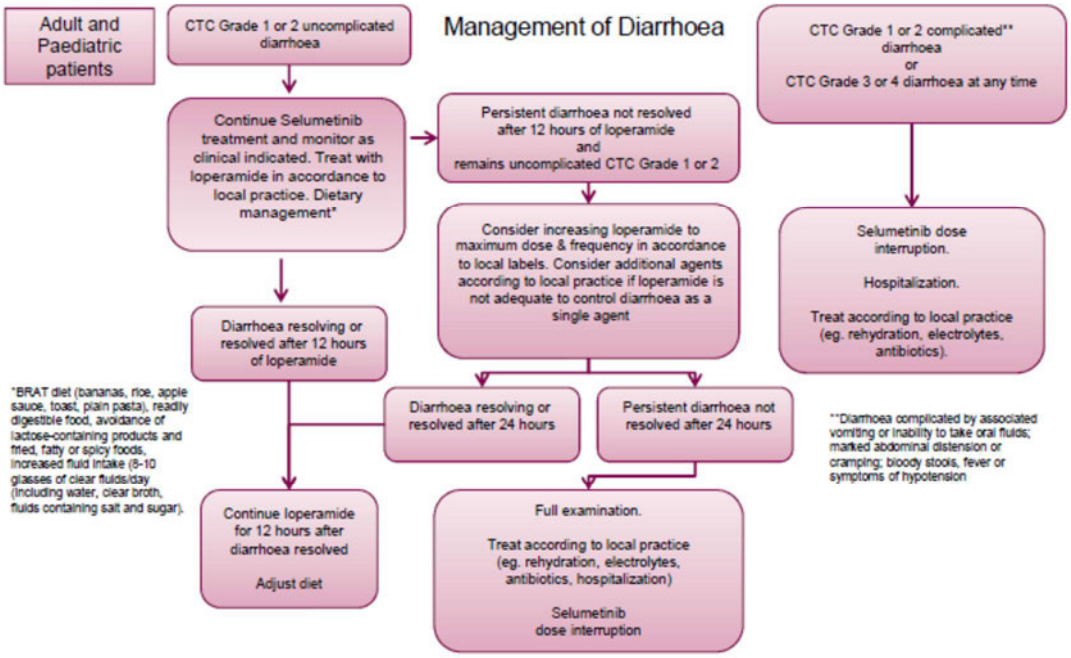

CK, creatine kinase; CTC Common Terminology Criteria; ULN, Upper Limit of Normal.

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



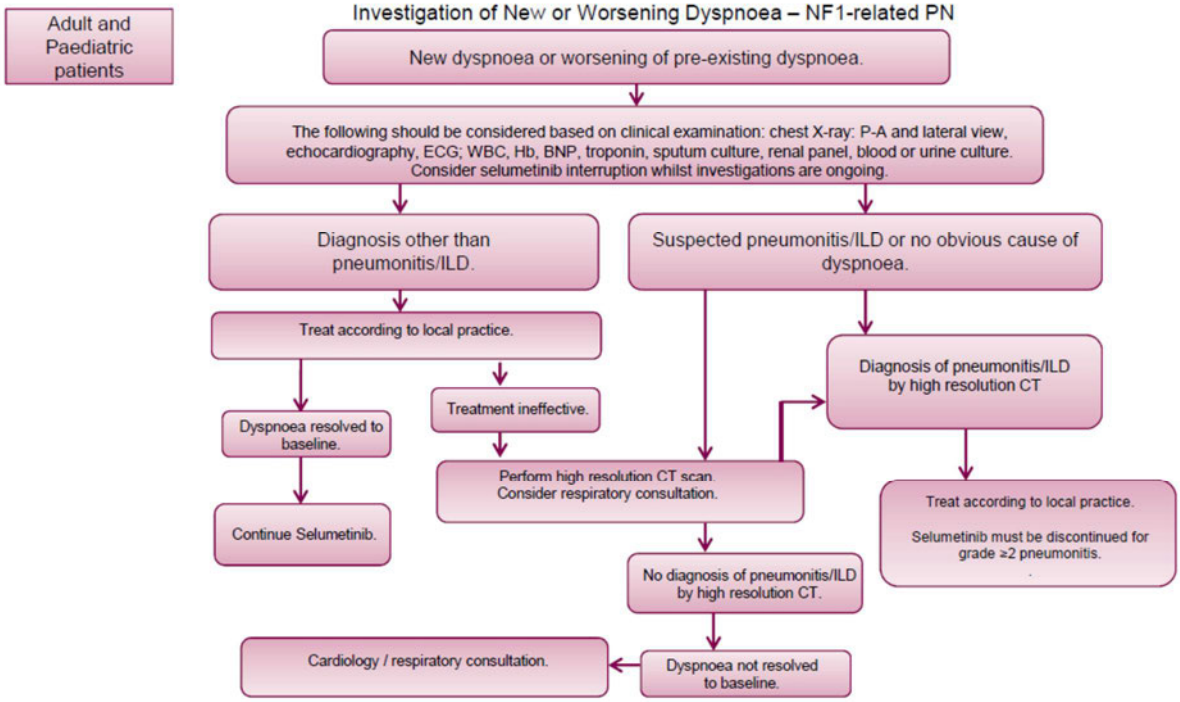

CSR, central serous retinopathy; RPED, retinal pigment epithelial detachment; RVO, retinal vein occlusion

# H 4 Management of Diarrhoea




CTC, Common Terminology Criteria

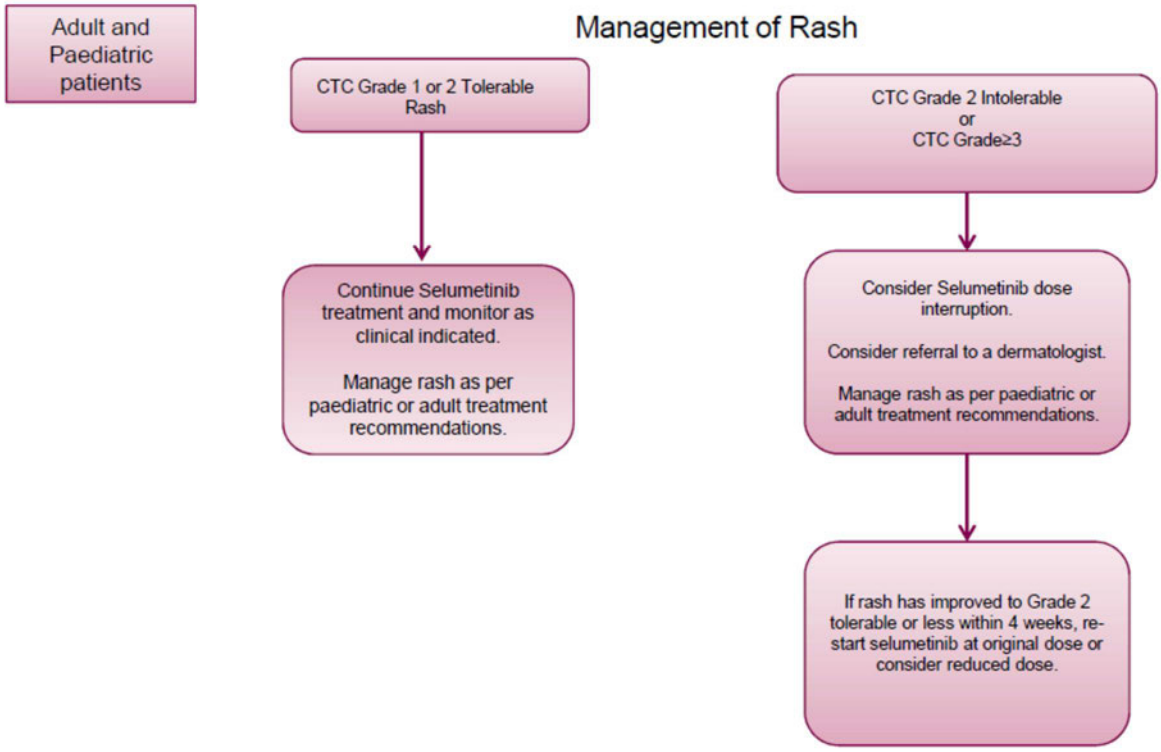
# H 5 Management of New or Worsening Dyspnoea



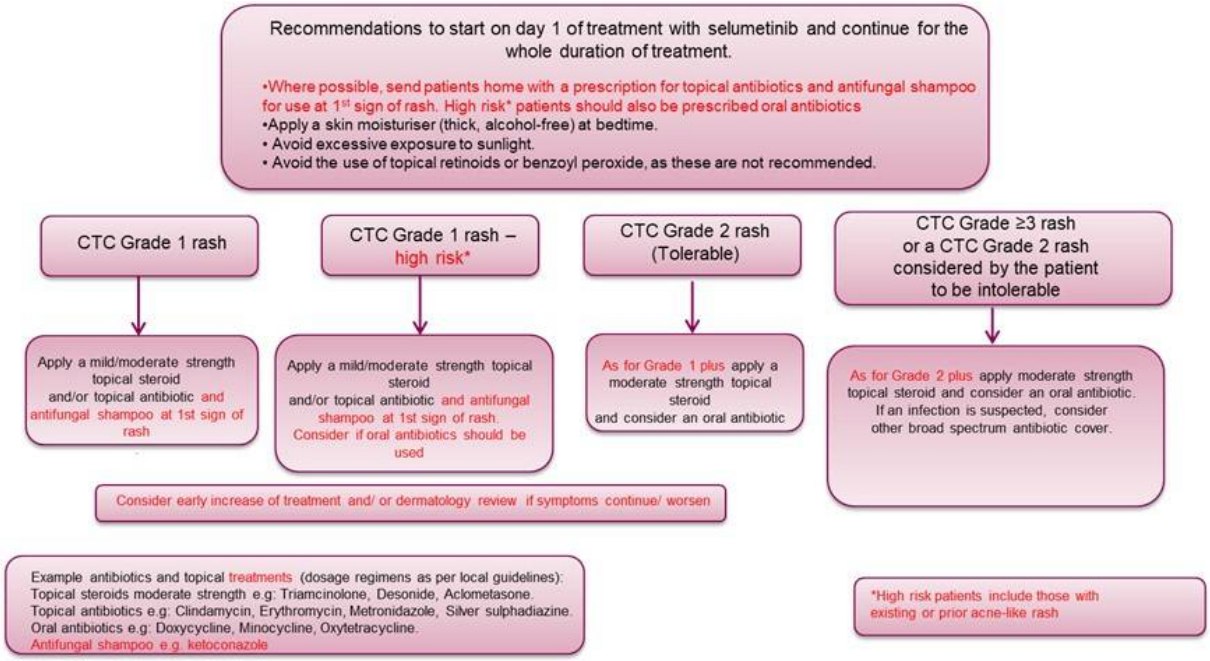

BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; Hb, haemoglobin; ILD, interstitial lung disease; P-A, posterior-anterior; WBC, white blood cell

# H 6 Management of Participants with Rash

## H 6.1 Management of Rash



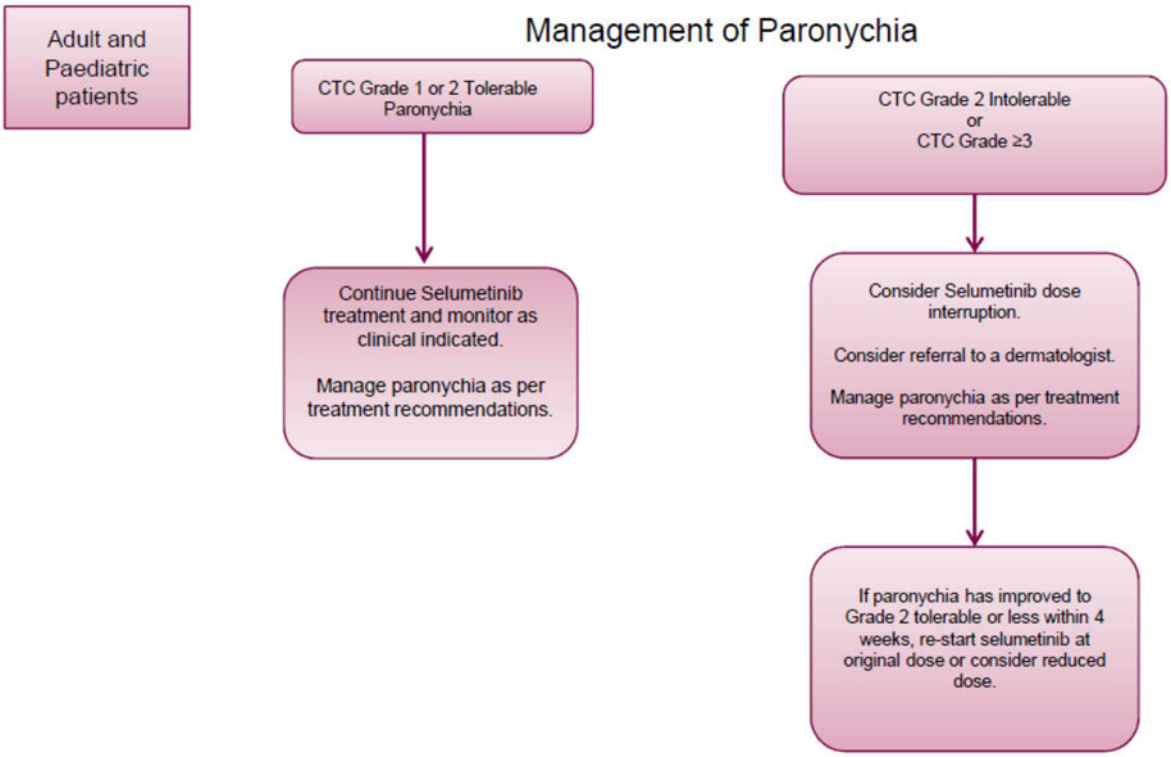

## H 6.2 Rash: Adult Treatment Recommendations



## H 7 Oral Care Management for Events of Oral Mucositis and Dry Mouth

- Participants should be encouraged to follow a daily oral health care regimes, both before and during treatment with selumetinib.
- Participants with a healthy mouth may use non-alcoholic mouthwash 4 to 6 times daily (eg, 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 tooth brushing (eg, after tea).
- Use of a mouthwash immediately after selumetinib intake is recommended.
- The tongue can be gently brushed (if not sore) with a soft toothbrush.
- Participants 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 participant 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). Participants with stomatitis should change their toothbrush every 4 to 6 weeks.
- Consider culture to rule out herpes simplex.
- Consider treating stomatitis at an early stage (CTCAE Grade 1) or as soon as the participant complains of a sore mouth. Consider using an oral topical analgesic, with or without topical steroids, depending on the participant's clinical condition and the local standard medical practice.

# H 8 Management of Paronychia




CTC, Common Terminology Criteria

**Table H12 Treatment Recommendations for AE Paronychia [a]**

| Severity | Treatment Recommendations |
|---|---|
| CTCAE Grade 1 | Treat the affected area by soaking in vinegar solution twice daily (1 part vinegar to 2 parts water) and 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) and systemic antibiotic (Keflex, Clindamycin) and 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 and drainage or surgical management. |

[a] If granulation tissue present, consider use of silver nitrate under supervision.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events

For participants 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 (eg, pyogenic-granuloma-like lesions). If the periungual skin is swollen but intact (whether infectious or non-infectious), silver nitrate is not recommended.

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

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

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

# Appendix I Cardiovascular Grading

## Table I13 Canadian Cardiovascular Society Grading of Angina Pectoris

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

## Table I14 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 J Concomitant Medications

## J 1 Guidance Regarding Potential Interactions with Concomitant Medications

Throughout the study, participants should avoid changes to, or the addition of, all concomitant medications and, in particular, any that may affect the metabolism of selumetinib (eg, CYP2C19 or CYP3A4 moderate/strong inhibitors, as well as CYP3A4 moderate/strong inducers), unless considered clinically indicated. The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

Strong or moderate **inducers** of CYP3A4 are not allowed at any time during the study. During the first cycle concomitant use of **strong or moderate inhibitors of CYP3A4 or CYP2C19,** with the exception of chronic PN pain medication, should be avoided until after the PK assessment. During the remainder of the study, if concomitant use of selumetinib with strong or moderate CYP3A4 or CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Table J15. For chronic PN pain medication fulfilling the above criteria, selumetinib should be initiated at a reduced dose as shown in Table J15. The dose of selumetinib should be reduced for the duration of concomitant therapy with the strong or moderate CYP3A4 or 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.

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, furosemide benzylpenicillin, baricitinib and tenofovir) cannot be excluded and they should be administered with caution.

**Table J15 Recommended Dosage of Selumetinib for Co-administration with Strong or Moderate CYP2C19 or CYP3A4 Inhibitors**

| BSA ($m^2$) | If the current dosage is up to 25 mg/$m^2$ bid, reduce to 20 mg/$m^2$ bid | | If the current dosage is up to 20 mg/$m^2$ bid, reduce to 15 mg/$m^2$ bid | |
|---|---|---|---|---|
| | 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 |

bid, twice daily; BSA, body surface area; CYP, cytochrome P450.

Changes to, or addition of medications detailed in Table J16 and Table J17 should be avoided, unless clinically indicated. The lists in Table J16 and Table J17 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 J16 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 bid [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 |

## Table J16 Inhibitors of CYP2C19 or CYP3A4 that AstraZeneca Recommends not to be Combined with Selumetinib

| 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 bid) 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.

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

**Table J17 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 |
| | Etravirine |
| | Elagolix |
| | Sotorasib |
| | Telotristat ethyl |
| | Nevirapine |

CYP, cytochrome P450.

## J 2 Restricted, Prohibited, and Permitted Concomitant Medications/Therapies

Restricted and prohibited concomitant medications/therapies are described in Table J18. Refer also to the dose modification guidelines for management of study intervention-related toxicities in Section 6.6.

**Table J18 Restricted and Prohibited Medications/Therapies**

| 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.<br><br>Not allowed during the study. |
| MEK inhibitor | Prior exposure is prohibited.<br><br>Not allowed during the study (with the exception of selumetinib study intervention). |

## Table J18 Restricted and Prohibited Medications/Therapies

| Prohibited medication/class of drug | Usage (including limits for duration permitted and special situations in which it is allowed) |
|---|---|
| Other systemic PN target treatment (including chemotherapy, immunotherapy, targeted therapy, biologic therapy, or monoclonal antibodies) | Not allowed for 4 weeks or 5 half-lives (whichever is longer) prior to the first dose of study intervention.<br><br>Not allowed during the study. |
| Radiotherapy | Not allowed for 6 weeks prior to the start of study intervention.<br><br>Radiotherapy (before or during the study) not allowed on target or non-target PNs. |
| Growth factors | Not allowed within the 7 days prior to screening assessment. |
| Blood transfusion (red blood cells or other blood products) | Not allowed within the 28 days prior to screening assessment. |
| Multivitamins containing vitamin E | Must be stopped 7 days prior to initiation of study intervention.<br><br>Not allowed during the study. |
| Herbal supplements or medications known to be strong or moderate inhibitors or inducers of CYP3A4 or strong or moderate inhibitors of CYP2C19. Substrates of OAT3. | Must be safely discontinued at least 14 days or 5 half-lives (whichever is longer) before the first dose of study intervention.<br>Strong or moderate inducers of CYP3A4 are not allowed at any time during the study. During the first cycle, concomitant use of strong or moderate inhibitors of CYP3A4 or CYP2C19 should be avoided until after the PK assessment. During the remainder of the study, if concomitant use of selumetinib with strong or moderate CYP3A4 or CYP2C19 inhibitors is not avoidable, then the selumetinib dose should be reduced as shown in Table J15. The dose of selumetinib should be reduced for the duration of concomitant therapy with the strong or moderate CYP3A4 or 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.<br>Selumetinib may affect the plasma/serum concentrations of substrates of OAT3 and they should be given with caution. |

CYP, cytochrome p450; IMP, investigational medicinal product; MEK = mitogen activated protein kinase; OAT3, organic anion transporter 3; PN, plexiform neurofibroma.

# 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 AstraZeneca 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 5.3 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 1 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 (ie, Indications, Contraindications, Warnings and Precautions, Adverse Reactions) on its use in the study population.

For patients with flexibility as to when to be enrolled in an AstraZeneca-sponsored study, vaccination prior to first dose of the trial investigational product(s) may be advisable.

Please contact the individual COVID-19 vaccine manufacturer if you have any questions concerning their product.

To better assess the overall impact of COVID-19 vaccination on a particular study and study population, ensure that both the COVID-19 vaccination details (including brand name and manufacturer) is captured in the eCRF as concomitant medication, and adverse reactions are reported.

Note: In Germany other non-PI tasks of HCP/TPV are not described in the CSP but in the main Local ICF Part I, Section 11-d (for example reaching out to patients to ask opinions on the Thank You card and Trial Result Summary, payment of patient expenses/compensation, optional telephone interview, management of accounts for Apps/devices, or in case of COVID-19 pandemic, possible additional services may be implemented e.g. drug courier services).

# Appendix L Abbreviations

| Abbreviation or Special Term | Explanation |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| aPTT | Activated partial thromboplastin time |
| AST | Aspartate aminotransferase |
| AUC | Area under the concentration-time curve |
| AUC(0-6) | Area under the concentration-time curve from time 0 to 6 hours |
| AUC(0-8) | Area under the concentration-time curve from time 0 to 8 hours |
| AUC(0-12) | Area under the concentration-time curve from time 0 to 12 hours |
| AUClast | Area under the concentration-time curve from time 0 to the last quantifiable concentration |
| bid | Twice daily |
| BP | Blood pressure |
| BSA | Body surface area |
| CRF | Code of Federal Regulations |
| CI | Confidence interval |
| CK | Creatine kinase |
| CK-MB | Creatine kinase-myocardial band |
| CK-MM | Creatine kinase-muscle |
| CL/F | Apparent total body clearance of the drug from plasma after extravascular administration |
| Cmax | Maximum observed concentration |
| COA | Clinical Outcome Assessment |
| CR | Complete response |
| CRO | Contract research organisation |
| CSP | Clinical study protocol |
| CSR | Central serous retinopathy |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTIS | Clinical Trials Information System |
| CV | Coefficient of variation |
| CYP | Cytochrome P450 |
| DCO | Data cut-off |
| DES | Data entry site |
| DILI | Drug-induced liver injury |
| DoR | Duration of response |

| Abbreviation or Special Term | Explanation |
|---|---|
| e-Diary | Electronic diary |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EMA | European Medicines Agency |
| EoT | End of Treatment |
| ePRO | Electronic patient-reported outcomes |
| EQ-5D-5L | EuroQol 5-Dimension 5-level |
| EQ-VAS | EuroQol visual analogue scale |
| ERK | Extracellular signal-regulated kinase |
| EU | European Union |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GRAD | Global Retention and Disposal Standard |
| GTPase | Guanosine 5'-triphosphatase |
| Hb | Haemoglobin |
| HCP | Health Care Professional |
| HIV | Human Immunodeficiency Virus |
| HL | Hy's Law |
| HRQoL | Health-related quality of life |
| IATA | International airline transportation association |
| ICF | Informed consent form |
| ICH | International Conference on Harmonisation |
| ICR | Independent central review |
| IEC | Independent Ethics Committee |
| 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 |

| Abbreviation or Special Term | Explanation |
|---|---|
| IRT | Interactive Response Technology |
| IT | Information technology |
| LLN | Lower limit of normal |
| LLOQ | Lower limit of quantification |
| LPD | Last participant dosed |
| LVEF | Left ventricular ejection fraction |
| LVSD | Left ventricular systolic dysfunction |
| Max | Maximum |
| MedDRA | Medical Dictionary for Regulatory Activities; |
| MEK | Mitogen activated protein kinase |
| MMRM | Mixed model repeated measures |
| MPAUC | Metabolite: parent ratio based on AUC |
| MPCmax | Metabolite: parent ratio based on Cmax |
| MPNST | Malignant peripheral nerve sheath tumours |
| MRI | Magnetic resonance imaging |
| MTP | Multiple testing procedure |
| n | Number |
| NCI | National Cancer Institute |
| NE | Not evaluable |
| NF1 | Neurofibromatosis type 1 |
| NIH | National Institutes of Health |
| NIMP | Non investigational medicinal product |
| NRS-11 | Numerical Rating Scale-11 |
| OAT3 | Organic anion transporter 3 |
| ORR | Objective response rate |
| PAINS-pNF | PAin INtensity Scale for plexiform neurofibromas |
| PBMC | Peripheral blood mononuclear cells |
| PedsQL | Paediatric Quality of Life Inventory |
| PD | Progressive disease |
| pERK | Phosphorylated extracellular signal-regulated kinase |
| PFS | Progression free survival |
| PGIC | Patients Global Impression of Change |
| PGIS | Patients GLOBAL Impression of Severity |
| PHL | Potential Hy’s Law |
| PK | Pharmacokinetic(s) |

| Abbreviation or Special Term | Explanation |
|---|---|
| PlexiQoL | Plexiform Neurofibroma Quality of Life scale |
| PN | Plexiform neurofibroma |
| PR | Partial response |
| PRO | Patient-Reported Outcomes |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | Preferred term |
| PTT | Partial thromboplastin time |
| QTcF | QTc interval as corrected by Fridericia's formula |
| REiNS | Response Evaluation in Neurofibromatosis and Schwannomatosis |
| RNA | Ribonucleic acid |
| RPED | Retinal Pigment Endothelial Detachment |
| RT-PCR | Reverse transcription polymerase chain reaction |
| RVO | Retinal vein occlusion |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SD | Standard deviation |
| SMQ | Standardised MedDRA query |
| SoA | Schedule of Activities |
| TBL | Total bilirubin |
| tlast | Time of last observed concentration |
| tmax | Time to reach maximum observed concentration following drug administration |
| TPV | Third Party Vendor |
| TTP | Time to progression |
| TTR | Time to response |
| ULN | Upper limit of normal |
| US | United States |
| VAS | Visual analogue scale |
| $VO_2$ | Maximal oxygen uptake |
| Vss/F | Volume of distribution (apparent) at steady state after extravenous administration |
| 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 TOC.

### Amendment 1.0 (Version 2.0): (25 January 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 revise the primary objective to be comparative relative to placebo, as requested by the FDA. A consequence of this update is an increase in the duration of treatment prior to crossover from placebo to selumetinib. The interim analysis has been revised. 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 |
|---|---|---|
| Section 1.1, Synopsis, Section 3, Table 4, Objectives and Endpoints, Section 9.1, Statistical Hypotheses, Section 9.2, Sample Size Determination, Section 9.4, Statistical Analyses | Changed primary endpoint of ORR assessment to be a formal hypothesis test comparing selumetinib versus placebo.<br>Moved previous primary endpoint of single-arm ORR assessment of selumetinib to be a secondary endpoint.<br>Updates to statistical analyses sections including MTP to reflect change. | FDA recommendation |
| Section 1.1, Synopsis, Section 4.1, Overall Design, and throughout | Additional DCO added | Due to the revision of the interim analysis |
| Section 1.1, Synopsis, Section 4.1, Overall Design, and throughout | Increase duration of placebo-controlled period from 8 cycles to 12 cycles | To allow robust comparison of ORR between treatment arms by end of Cycle 16 landmark |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, Synopsis, Section 4.1, Overall Design, Section 4.2 Scientific Rationale for Study Design Section 9.1, Statistical Hypotheses, Section 9.4.2.1.3 Analysis Methods | Timing of primary analysis changed from 12 months post LPD to landmark analysis by end of 16 cycles | At least 16 cycles of follow up is required to perform a meaningful comparison of ORR on selumetinib vs placebo |
| Section 1.3, Schedule of Assessments, Table 1 and Table 2 | Additional timepoints for PGIS/PGIC, investigator assessment of changes in pain medication, AEs, and concomitant mediations added | Due to increased duration of placebo-controlled period |
| Section 1.3, Schedule of Assessments, Table 1 and Section 8.2.6, Clinical Safety Laboratory Assessments | Pregnancy tests changed to every cycle throughout, instead of at each visit | Study population is adults including women of child-bearing potential, which differs from previous studies that were carried out in a paediatric population |
| Section 1.1, Synopsis, Section 4.1, Overall Design, Section 9.2, Sample Size determination | Added that if it is anticipated that 20% or more of participants withdraw prior to the end of Cycle 16 , for reasons other than progression, then recruitment rates withstanding, enrolment will continue to randomise at least 50% of the total number of drop-out participants | To ensure the primary endpoint is adequately powered |
| Section 5.1, Inclusion Criterion 2 | Updated NF1 diagnostic criteria | To align with the most recent published guidance (Legius et al 2021) |
| Section 9.5, Interim Analyses | Amended interim analysis | To provide earlier data with good power on the primary and key secondary endpoint |

AE, adverse event; DCO, Data cut-off; FDA, Food and Drug Administration; LPD, Last participant dosed; NF1, Neurofibromatosis type 1; ORR, Objective response rate; MTP, Multiple testing procedure; PGIC, Patients Global Impression of Change; PGIS, Patients GLOBAL Impression of Severity.

## Summary of Non-substantial Changes

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.3, Schedule of Assessments, Table 1 | Footnote 'o': Added that all volumetric MRI scans should be performed relative to Cycle 1 Day 1, ie the time course should not change if the participant experiences a dose interruption or there are delays in previous scan visits<br>Footnote 'e' amended to add results of any previous genetic testing for NF1 to disease characteristics.<br>Updated general footnote to state "Participant's second dose on the day of their on-site visit can be taken from newly dispensed study intervention" | Clarification |
| Section 1.1, Synopsis, Section 3, Table 4, Objectives and Endpoints | Added that measurable target PN at baseline is per ICR and clarified analysis populations | Clarification |
| Section 1.1, Synopsis, Section 3, Table 4, Objectives and Endpoints | Added PFS evaluation during the randomised period as an exploratory endpoint | For additional information |
| Section 1.1, Synopsis, Section 3, Table 4, Objectives and Endpoints | Removal of "as assessed by the investigator" for the exploratory objective of long-term assessment of pain medication compared to baseline | Assessment not relevant as data are only collected during the randomised period |
| Section 1.1 Synopsis, Section 3, Table 4, Objectives and Endpoints | Added an exploratory objective to investigate NF1 mutation alteration patterns | For additional information |
| Section 2.2 Background and Section 8.1.8.1 PAINS-pNF | Added definition for chronic PN pain and spikes of PN pain | Clarification |
| Section 4.1, Overall Design | Final analysis wording changed from 24 months post LPD to 24 cycles post LPD | Clarification |
| Section 5.2, Exclusion Criterion 3 | Updated optic glioma criterion | Clarification |
| Section 5.2, Exclusion Criterion 12 | Clarified that prosthesis or orthopaedic or dental braces should not be in close proximity to the area of interest | Clarification |
| Section 5.2, Exclusion Criterion 17 | Corrected restriction of CYP2C19 inducers | Clarification |
| Section 5.3, Screen Failures | Clarified that participants can be rescreened if failure was for a technical reason and amended wording describing reason for withdrawal to match eCRF | Clarification |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1, Synopsis, Section 4.1, Overall Design, Section 6.1.1, Investigational Products | Clarified that following crossover to selumetinib treatment, treatment will be open-label | Clarification |
| Section 1.1, Synopsis, Section 6.1.1, Investigational Products | Clarification that unblinded open label stock will be dispensed to the participant following crossover added | Clarification |
| Section 6.1.1, Investigational Products | Guidance provided for when a dose is missed or if vomiting occurs | To provide guidance |
| Section 6.3, Measures to Minimise Bias: Randomisation and Blinding, Section 7.2, Participant Withdrawal from the Study | Clarification that emergency unblinding leads to discontinuation from the study | Clarification |
| Section 6.5, Concomitant Therapy Appendix J, Concomitant Medication | Removed the restriction for CYP2C19 inducers, updated the guidance for CYP2C19 inhibitors as well as the lists of example inhibitors and inducers | To correct an error and provide most recent guidance |
| Section 6.5, Concomitant Therapy Appendix J, Concomitant Medication | Included guidance on substrates of OAT3 | Although selumetinib does not meet the criteria for OAT3 inhibition according to FDA guidance, it does for European Medicines Agency guidance |
| Section 8.1.1 Imaging of the Target PN, Section 8.1.2 Independent Central Review of Scans, Section 9.4.2.1.1 Calculation of PN Assessment | Included additional guidance on MRI scans (Section 8.1.1) and removed reference to Independent Review Charter | Document not relevant to Investigator |
| Section 8.1.8.9, Administration of ePRO Questionnaires | Added that paper questionnaires are allowed in exceptional circumstances | To allow a back-up process if required |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 8.1.8.10 Qualitative Participant Interviews | Updated number of participants | Update |
| Section 8.2.6 Clinical Safety Laboratory Assessments, Table 8 | Updated footnote to clarify reporting of aPTT and PTT tests and added footnotes to clarify reporting of leukocyte differential count (absolute count) urea nitrogen and blood urea nitrogen | Clarification |
| Section 8.3.2, Follow-up of AEs and SAEs | Clarified information collected on grade of AEs | Clarification |
| Section 9.3, Populations for Analysis | Updates to populations to reflect change in primary objective, to include Measurable PN FAS analysis population and to clarify analysis populations | Clarification |
| Section 9.4.1, General Considerations | Added definition of randomised period | Clarification |
| Section 9.4.2.2, Key Secondary Endpoint | Geographical region added as a baseline covariate and clarified chronic pain medication use is based on e-Diary and investigator's assessment of pain medication | Clarification |
| Section 1.1, Synopsis, Section 9.4.2.2, Key Secondary Endpoint, Section 9.4.2.3.7 Chronic Target PN Pain Palliation | Clarified that average cycle PAINS-pNF chronic target pain score will only be derived if the participant meets the criteria of having at least 4 daily pain scores out of 7 days for at least 3 non-overlapping 7-day periods in the 28-day cycle | Clarification |
| Section 9.4.2.3 Secondary Endpoints | Clarified populations for analysis | Clarification |
| Section 9.4.2.3.2, Duration of Response, Section 9.4.2.3.4, Time to Progression, Section 9.4.2.3.5, Time to Response, Section 9.4.2.3.6, Best Percentage Change from Baseline in Target PN | Clarified that the analysis will include all participants randomised to study intervention with measurable target PN at baseline per ICR. | Clarification |
| Section 9.4.3.1 Adverse Events | Removed "High level term" from the presentation of AEs | Not standard |
| Section 9.4.3.5 Other Safety Endpoint(s) | Removed summarisation of physical examination data | Not required |

| Section Number and Name | Description of Change | Brief Rationale |
|---|---|---|
| Section 1.1 Synopsis, Section 9.4.4.1 Pharmacokinetics, Section 3, Table 4, Objectives and Endpoints | Aligned description of PK parameters to AstraZeneca standards and SAP and removed detailed descriptions included in SAP | Clarification |
| Appendix G3 | PROMIS Item Bank updated | Correction |
| Throughout protocol | PAIN-pNF amended to PAINS-pNF (PAin INtensity Scale for plexiform neurofibromas). | Renaming of the PAIN-pNF tool by the NCI |

AE, adverse event; aPTT, Activated partial thromboplastin time; eCRF, Electronic case report form; FAS, Full Analysis Set; FDA, Food and Drug Administration; ICR, Independent central review; LPD, Last participant dosed; MRI, Magnetic resonance imaging; NF1, Neurofibromatosis type 1; PAINS-pNF, PAin INtensity Scale for plexiform neurofibromas; PK, Pharmacokinetics; PFS, Progression free survival; PN, Plexiform neurofibroma; PROMIS, Patient-Reported Outcomes Measurement Information System; PTT, Partial thromboplastin time; SAP, statistical analysis plan.

# Appendix N Country Specific Requirements

European Union Country Specific Requirements

| Section # and Name | Description of Change with Reason |
|---|---|
| Section 4.5 Study Conduct Mitigation during Study Disruptions due to Cases of Civil Crisis, Natural Disaster, or Public Health | In accordance with Local Regulatory Authority requirements, it's specified that in Germany 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) there will be no verbal consenting.<br>Consent is obtained in writing |
| Appendix K Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis | In accordance with Local Regulatory Authority requirements, it's specified that in Germany other non-PI tasks of HCP/TPV are not described in the CSP but in the main Local ICF Part I, Section 11-d (reach out to patients to ask opinion for Thank You card and Trial Result Summary, payment of patient expenses/compensation, optional telephone interview, manage accounts for Apps/devices, or in case of COVID-19 pandemic, possible services may be implemented e.g. drug courier services). |
| Section 8.3.9. Deaths<br><br>Section 8.3.12 Reporting of Serious Adverse Events<br><br>Section 8.3.14.1 Timelines<br><br>Section 8.4 Overdose | In Germany SAE reporting has to be done immediately without undue delay after obtaining knowledge. |

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