STATISTICAL ANALYSIS PLAN

Study Code D1346C00004 Edition Number 3.0

Date 29 April 2024

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

List abbreviations and definitions of specialised or unusual terms, measurements, or units.

Examples are provided below. These can be modified at study level.

Abbreviation or Specialized Term	Definition
AE	Adverse event
ADaM	Analysis Dataset Model
ADLB	Laboratory Test Result Analysis dataset
ALT	Alanine aminotransferase
AM	Ante Meridiem
AESI	Adverse event of special interest
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUClast	Area under the concentration-time curve from 0 to the last quantifiable concentration
AUC0-6	Partial area under the concentration-time curve from time 0 to 6 hours
AUC0-12	Partial area under the concentration-time curve from time 0 to 12 hours
AUC0-24	Partial area under the concentration-time curve from time 0 to 24 hours
CCI	CCI
BN	BSA normalised
BOR	Best objective response
BSA	Body surface area
cCR	Confirmed complete response
CI	Confidence interval
CL/F	Apparent total body clearance of drug from plasma after extravascular administration
Cmax	Maximum observed concentration
CMT	Clinically meaningful threshold
COA	Clinical outcome assessment
COVID-19	Coronavirus disease 2019
cPR	Confirmed partial response
CR	Complete response
CRF	Case report form
CRO	Contract Research Organisation

CSP	Clinical study protocol
CSR	Clinical study report
CSRHLD	Clinical Study Report or High-Level Document
CTCAE	Common Terminology Criteria for Adverse Events

CCI	CCI
DCO	Data cut-off
DCO1	first DCO
DCO2	second DCO
DCO3	third DCO
DN	Dose normalised
CCI	CCI
ECG	Electrocardiogram
ECHO	Echocardiogram
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
gSD	Geometric standard deviation
CCI	CCI
ICF	Informed consent form
ICR	Independent central review
IPD	Important protocol deviation
IRC	Independent Review Charter

CCI	CCI
LLOQ	Lower limit of quantification
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
MPAUC0-6	Metabolite:parent ratio based on AUC0-6
MPAUC0-12	Metabolite:parent ratio based on AUC0-12
MPAUC0-24	Metabolite:parent ratio based on AUC0-24
MPCmax	Metabolite:parent ratio based on Cmax
MRI	Magnetic resonance imaging
NA	Not applicable
NCA	Non-compartmental PK analysis
NE	Not evaluable
NF1	Neurofibromatosis Type 1
NSAIDs	Non-steroidal anti-inflammatory drugs
OAE	Other significant adverse event
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
CCI	CCI
pERK	Phosphorylated extracellular signal regulated kinase
CCI	CCI
PK	Pharmacokinetics
PM	Post Meridiem
PN	Plexiform neurofibromas
PR	Partial response
QTcB	QT interval corrected by Bazett's method
QTcF	QT interval corrected by Fridericia's method
Q1	1st quartile

Q3	3rd quartile
RacAUC0-12	Accumulation ratio for AUC0-12
RacCmax	Accumulation ratio for Cmax
RDI	Relative dose intensity
REiNS	Response Evaluation in Neurofibromatosis and Schwannomatosis
REML	Restricted maximum likelihood
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
CCI	CCI
SRC	Safety Review Committee
TELC	Treatment-emergent laboratory change
TFL	Tables, figures, and listings
tmax	Time to reach the maximum observed concentration
CCI	Time to progression
CCI	Time to response
t½λz	Half-life associated with the terminal slope of the concentration-time curve
ULN	Upper limit of normal
VMI	Visual-motor integration
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration
Vz/F	Volume of distribution (apparent) based on the terminal phase following extravascular administration
WHO	World Health Organization

AMENDMENT HISTORY

CATEGORY Change refers to:	Date	Description of change	In line with CSP?	Rationale
N/A	07Jun2022	Initial approved SAP	N/A	N/A
List of Abbreviations	05Dec2023	Added NCA	Yes	Reference for abbreviation NCA to be included
Section 1 Introduction	05Dec2023	Updated text to mention that this SAP is based on Amendment 3 of the CSP (version 4.0) dated 14 February 2023	Yes – v4.0	Aligned SAP to CSPv4.0
Section 1.1 Study Design	05Dec2023	Updated text for dose-finding phase and SRC reviews	Yes – v4.0	Aligned SAP to CSPv4.0
Section 3.1 Timing of Analyses	05Dec2023	Added treatment compliance to Table 1 (summary of outcome variables and timing of analyses)	Yes	Addition of treatment compliance to align with company standards
Section 3.2.2 Pharmacokinetic Analysis Set	05Dec2023	Updated text to add clarity on the definition of the PK Analysis Set	Yes - v4.0	Aligned the definition in SAP to the definition in CSP. In addition, provided clarity on the process of defining the PK Analysis Set
Section 3.2.4 Summary of Outcome Variables and Analysis Sets	05Dec2023	Added treatment compliance to Table 2 (summary of outcome variables and analysis sets)	Yes	Addition of treatment compliance to align with company standards

Section 4 Statistical Analysis	05Dec2023	Added text 'The starting dose schema was approved by the SRC as the recommended dose schema at the end of the dosefinding phase.' Removed the planned analysis by global analysis, pooled analysis, and PK analysis. Replaced with a more streamlined approach (presented for the Global Cohorts [Global Cohort 1, Global Cohort 2, both Global Cohorts combined, the Japan Cohort, and for all participants (all cohorts combined)], except for the PK analyses where the Global Cohorts and the Japan	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to several dose schema is no longer required.

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
		Cohort will be presented separately without combining).		
Section 4.1 Study Population	05Dec2023	Deleted text 'and study drug compliance'	Yes	The study intervention compliance will be presented with the exposure data in alignment with company standard oncology templates.
Section 4.1.5.1 Presentation	05Dec2023	Added in BSA group for granulation formulation dose schema for selumetinib	Yes	Provided definition and clarity on the BSA groups to be used for granule formulation dose schema
Section 4.2 Endpoint Analyses	05Dec2023	Added text to mention CCI [redacted] and CCI [redacted] analyses will be reported separately	Yes	CCI [redacted] and CCI [redacted] exploratory analyses will not form part of the clinical study report.

Section 4.2.1.1 Primary Analysis of the Primary Endpoint	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.1.2 Supplementary Analyses of the Primary Endpoint	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.5.7 Primary Analysis of the Secondary Endpoint	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.5.9 Supplementary Analyses of the Secondary Endpoint	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
				recommended dose schema is no longer required.
Section 4.2.6.3 Primary Analysis of CCI	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.

Section 4.2.7.3 Primary Analysis of CCI	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.8.3 Primary Analysis of CCI	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.9.3 Primary Analysis of CCI	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.10.4 Analysis of CCI	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.11.3 Analysis of	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
CCI				recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.

Section 4.2.12.3 Analysis of CCI [redacted]	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.13.2 Analysis of CCI [redacted]	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.14.3 Analysis of CCI [redacted]	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.2.15.2 Analysis of the CCI [redacted]	05Dec2023	Removed reference to the recommended dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the recommended dose schema is no longer required.
Section 4.4.2.1 Plasma Concentrations	05Dec2023	Removed reference to the dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the dose schema is no longer required.

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**

Section 4.4.2.2 Pharmacokinetic Parameters	05Dec2023	Removed reference to the dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the dose schema is no longer required.
Section 4.4.2.3 Graphical Presentation	05Dec2023	Removed reference to the dose schema	Yes	The starting dose was approved by the SRC as the recommended dose schema at the end of the dose-finding phase for both cohorts. Reference to the dose schema is no longer required.
Section 4.6 Safety Analyses	05Dec2023	Updated text to include treatment compliance	Yes	Addition of treatment compliance to align with company standards
Section 4.6.1 Exposure and Treatment Compliance	05Dec2023	Updated text to include treatment compliance	Yes	Addition of treatment compliance to align with company standards
Section 4.6.1.1 Definitions and Derivations	05Dec2023	Updated text to include treatment compliance definition, derivation, and thresholds	Yes	Addition of treatment compliance to align with company standards
Section 4.6.1.2 Exposure: Presentation	05Dec2023	Updated text to include presentation of treatment compliance	Yes	Addition of treatment compliance to align with company standards
List of Abbreviations	14Dec2023	Added BOR and TFL	Yes	Reference for abbreviations BOR and TFL to be included
Section 3.2.2 Pharmacokinetic Analysis Set	14Dec2023	Updated text to further add clarity on the PK Analysis Set	Yes	Provide clarity on the PK Analysis Set
Section 3.2.4 Summary of Outcome Variables and Analysis Sets	14Dec2023	Updated analysis population for safety for pharmacodynamic data in Table 2 (summary of outcome variables and analysis sets)	Yes	Not appropriate to conduct Pharmacodynamic analysis on the PK analysis dataset as optional different blood samples are taken
Section 3.3 General Considerations	14Dec2023	Updated text for precision of data presentations in bullet point 2	Yes	Updated to align with ADaM programming standards to ADLB
Section 3.3.6.3 Missing Death Dates	14Dec2023	Updated text to include the definition of the last date known to be alive	Yes	Updated for clarity on how the last date known to be alive

				will be imputed in the event of a missing death detail

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Section 3.3.10 Compliance Definition for Clinical Outcome Assessments	14Dec2023	Removed 'For compliance of palatability the participant will have complied if any of the first 3 items in section 4.2.3 are answered.'	Yes	Not required as palatability presents on completion rate rather than a defined compliance definition
Section 4.1.5.1 Presentation	14Dec2023	Added inequalities to make the BSA boundary cases clearer	Yes	Addition of inequalities for clarity on BSA boundary cases so it is clear which category each individual BSA will fall into
Section 4.1.8.2 Presentation	14Dec2023	Updated text to include "The individual participant data for subsequent PN therapy will also be listed."	Yes	Included for completeness
Section 4.2 Endpoint Analyses	14Dec2023	Updated population for pharmacodynamic analysis from PK to safety	Yes	Not appropriate to conduct Pharmacodynamic analysis on the PK analysis dataset as optional different blood samples are taken
Section 4.2.1.1 Primary Analysis of the Primary Endpoint	14Dec2023	Added wording "from single dose administration (cycle 1 day 1)."	Yes	Provided clarity for the primary endpoint analysis on single dose administration
Section 4.2.1.2 Supplementary Analyses of the Primary Endpoint	14Dec2023	Added wording "from single dose administration (cycle 1 day 1)."	Yes	Provided clarity for the primary endpoint analysis on single dose administration
Section 4.2.3.2 Derivations	14Dec2023	Changed "subjects" to "participants" in Items 4 and 5	Yes	Updated for consistency within the document
Section 4.2.5.6 Best Objective Response Definition	14Dec2023	Added a new section to clearly define the definition and derivation of BOR to be used in the analyses	Yes	Definition of BOR was previously missing so it was included for clarity and completeness on the definition and derivation for analyses

Section 4.2.5.7 Primary Analysis of the Secondary Endpoint	14Dec2023	Re-numbered from 4.2.5.6 due to the addition of new Section 4.2.5.6	Yes	Re-numbered due to new section being included
Section 4.2.5.8 Sensitivity Analyses of the Secondary Endpoint	14Dec2023	Re-numbered from 4.2.5.7 due to the addition of new Section 4.2.5.6	Yes	Re-numbered due to new section being included
Section 4.2.5.9 Supplementary Analyses of the Secondary Endpoint	14Dec2023	Re-numbered from 4.2.5.8 due to the addition of new Section 4.2.5.6	Yes	Re-numbered due to new section being included

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Section 4.2.6.3 Primary Analysis of CCI	14Dec2023	Updated text to "Additional graphical symbols to depict the start of objective response, PD or death, and subsequent therapy will be added. On treatment will be designated with different colour than posttreatment."	Yes	Aligned with the decision made for mock shells v1.0.
Section 4.2.11.3 Analysis of CCI	14Dec2023	Removed reference to item scores and total score to only present weekly average total scores in tables. All item scores will be listed.	Yes	Aligned with the previous discussions (Jan 2023) and decisions made for mock shells v1.0.
Section 4.2.12.3 Analysis of CCI	14Dec2023	Removed reference to item scores and total score to only present weekly average total scores in tables. All item scores will be listed.	Yes	Aligned with the previous discussions (Jan 2023) and decisions made for mock shells v1.0.
Section 4.4.1 Calculation or Derivation of Pharmacokinetic Parameters	14Dec2023	Added the sentence "The same analysis as described in Section 4.2.1.1 and Section 4.2.1.2 for the primary endpoint will be performed for N-desmethyl-selumetinib."	Yes	Clarified analysis methods to be conducted
Section 4.4.2.1 Plasma Concentrations	14Dec2023	Removed the sentence "The same analysis as described in Section 4.2.1.1 and 4.2.1.2 for the primary endpoint will be performed for N-desmethylselumetinib."	Yes	Moved to the correct section (ie, Section 4.4.1)

Section 4.4.2.3 Graphical Presentation	14Dec2023	Added tmax to selumetinib single dose and added AUC024 and tmax to N-desmethyl selumetinib single dose	Yes	Previously omitted in error
Section 4.6.1.1 Definitions and Derivations	14Dec2023	Updated wording from 'Total (or intended) exposure' to 'Duration of exposure'. Updated 'subject' to 'participant'. Updated 'Actual exposure' to 'Actual duration of exposure'. Updated 'total exposure' to 'duration of exposure'.	Yes	Provide clarity and consistency in terminology
Section 4.6.1.2 Presentation	14Dec2023	Updated wording from 'Total (or intended) exposure' to 'Duration of exposure'. Updated 'Actual exposure' to 'Actual duration of exposure'.	Yes	Provided clarity and consistency in terminology
Section 4.6.2.1 AE Definitions	14Dec2023	Added a sentence to explain why the long-term safety	Yes	Justified reason (as stated in CSP) for including long-term

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
and Derivations		follow-up is needed		safety follow-up in participants who are < 3 years of age at the start of dosing
Section 4.6.2.2 AE Presentation	14Dec2023	Updated text for AEs with an outcome of death and AEs with an outcome of death possibly related to intervention to report SAEs instead Updated text to include details and summaries on AEs occurring > 30 days after study intervention discontinuation	Yes	Previously omitted in error
Section 4.6.3.1 Definitions and Derivations	14Dec2023	Updated text for changes from baseline to make the text more concise	Yes	Updated text to align with the mock shell presentation and definitions and derivations
Section 4.6.7.2 Presentation	14Dec2023	Update text to include 'borderline'.	Yes	Updated text to align with the categories in the CRF
Section 4.6.11.2 Presentations	14Dec2023	Update text to "Shift tables showing score changes from baseline to worst score on treatment will be produced."	Yes	Updated to align the text with the presentation of analysis agreed in the mock shells
Section 3.2.1 Enrolled	20Dec2023	Updated title to 'Enrolled'	Yes	Updated to aligned with other Koselugo analysis plans

Section 4.1.1.1 Presentation	20Dec2023	Addition of a paragraph to include a description of the disposition tables due to global / country situation	Yes	Updated to include and provide completeness
Section 4.1.4.2 Presentation	20Dec2023	Removed repetition of the demographic summary table for all participants in the PK analysis set and safety analysis set	Yes	Unnecessary to include as all participants will be part of the PK analysis set and the safety analysis set
Section 4.1.5.1 Presentation	20Dec2023	Corrected a typographical error of 0.129 that should have read as 1.29	Yes	Correction of a typographical error
Section 4.2 Table	20Dec2023	Corrected population for the exploratory CCI analyses	Yes	Correction of a population error
Section 4.2.3.3 Analysis of Palatability	20Dec2023	Removed text relating to the bar chart presenting compliance categories	Yes	Removed as not necessary
Section 4.2.10.4 Analysis of CCI	20Dec2023	Removed text relating to the bar chart presenting compliance categories	Yes	Removed as not necessary
Section 4.2.11.3 Analysis of CCI	20Dec2023	Removed text relating to the bar chart presenting compliance categories	Yes	Removed as not necessary

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
Section 4.2.12.3 Analysis of CCI	20Dec2023	Removed text relating to the bar chart presenting compliance categories	Yes	Removed as not necessary
Section 4.2.13.2 Analysis of CCI	20Dec2023	Removed text relating to the bar chart presenting compliance categories	Yes	Removed as not necessary
Section 4.2.14.3 Analysis of CCI	20Dec2023	Removed text relating to the bar chart presenting compliance categories	Yes	Removed as not necessary
Section 4.4.2 Presentation of Pharmacokinetic Data	20Dec2023	Removed the last sentence about CCI analyses	Yes	Repeated elsewhere in the document

Section 4.4.2.1 Plasma Concentrations	20Dec2023	Added sentence about the feasibility of repeating outputs by BSA group	Yes	If each BSA group has too few observations to guarantee a meaningful analysis, then it will not be performed.
Section 4.4.2.2 Pharmacokinetic Parameters	20Dec2023	Added sentence about the feasibility of repeating outputs by BSA group	Yes	If each BSA group has too few observations to guarantee a meaningful analysis, then it will not be performed.
Section 4.6.1.2 Presentation	20Dec2023	Updated treatment compliance categories	Yes	Aligned with other Koselugo study treatment compliance categories
Section 4.6.2.2 Presentation	20Dec2023	Removed AE summaries for AE occurring > 30 days after study intervention discontinuation	Yes	Not necessary to be included and aligned with other Koselugo studies
Section 4.6.2.2 Presentation	20Dec2023	Removed summary by system organ class, preferred term, and causality	Yes	Not necessary, and data are available in other tables. Aligned with other Koselugo studies
Section 4.6.2.2 Presentation	20Dec2023	Removed the sentence on reporting overdose and medication error data	Yes	Not necessary, and data are available in other tables. Aligned to other Koselugo studies
Section 4.6.2.2 Presentation	20Dec2023	Added non-serious adverse events occurring in more than 5% of subjects	Yes	Necessary table that was omitted in error
Section 4.6.9.2 Presentation	20Dec2023	Added text to clarify the required by eye (left/right)	Yes	Provided clarity for presentations by eye
Section 4.2 Table	21Dec2023	Secondary ORR – included ORR in the population level summary	Yes	Necessary in the table that was omitted in error
Section 4.2 Table	21Dec2023	Added estimate LSMeans and	Yes	Provided clarity for MMRM

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
		associated CCI CI for MMRM in the population level summary for CCI [redacted]		presentation
Section 4.2.10.1 Definitions and Derivations	21Dec2023	Updated wording from ‘general’ to ‘generic’. Updated ‘questions’ to ‘items’.	Yes	Updated for consistency

Section 4.2.10.4 Analysis of CCI	21Dec2023	Updated paragraphs on MMRM to amend the terms to be included in the model. Updated MMRM model assumptions and process to conduct the model.	Yes	Provided clarity on how to conduct the MMRM and updated the terms to be included in the model to align with other Koselugo studies
Section 4.2.11.3 Analysis of CCI	21Dec2023	Added text for baseline terms to be used in the MMRM model	Yes	Provided clarity on how to conduct the MMRM and updated the terms to be included in the model to align with other Koselugo studies
Section 4.2.12.3 Analysis of CCI	21Dec2023	Added text for baseline terms to be used in the MMRM model	Yes	Provided clarity on how to conduct the MMRM and updated the terms to be included in the model to align with other Koselugo studies
Section 4.6.3.1 Definitions and Derivations	21Dec2023	Corrected link under Table 15	Yes	Correction of table link error
Section 4.4.2.1 Plasma Concentrations	10Jan2024	Added text for on-treatment BSA groups	Yes	Provided clarity on which BSA groups should be used for the PK data presentations
Section 4.4.2.2 Pharmacokinetic Parameters	10Jan2024	Added text for on-treatment BSA groups	Yes	Provided clarity on which BSA groups should be used for the PK data presentations
Section 4.4.2.3 PK Graphical Presentation	10Jan2024	Added text for on-treatment BSA groups	Yes	Provided clarity on which BSA groups should be used for the PK data presentations
Section 4.6.6.2 Presentation	10Jan2024	Updated text ‘weight/height’ to ‘BSA’ for individual plots. Added text for inclusion of BSA group in listings.	Yes	Added BSA group in listings, for clarity on reporting. Individual plots of BSA over time more meaningful than weight/height plots over time.
Writing and formatting QC	30Jan2024	Writing and formatting QC Checks by Synchrogenix	N/A	As per company standards
Section 1	29Apr2024	Updated CSP version	N/A	New version available
Section 1.1	29Apr2024	Minor changes in the study design description, including removal of minimum sample size of [redacted] for the Japanese cohort	No	To improve overall readability and to reflect early termination of recruitment with n=[redacted] patients

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**

Section 3.1	29Apr2024	Removed footnote "If there are any major variable changes in the database after the DCO, the outputs will be repeated at DCO2 and/or DCO3 (depending on the timing of the updates).	N/A	This will only occur in case of data issues found in the DCO1 CDL but we should not plan for it.
Section 3.2.2	29Apr2024	Clarification that IPDs affecting the PK may lead to the exclusion of some data points and not to the overall patient exclusion.	N/A	Clarification on the PK analysis set
Section 3.3.6	29Apr2024	Added sentence "If the imputed end date is after the date of study discontinuation, then the end date will instead be taken as the date of study discontinuation."	N/A	To follow AZ Standards
Section 3.3.9	29Apr2024	Added sentence "Except for the palatability test where if the subject it not on treatment or if the subject transitioned to capsules the COA is not expected.	N/A	To better clarify an exception
Section 3.3.10	29Apr2024	Clarification on how to calculate Expected number of entries and compliance by week	N/A	Better
Section 3.4	29Apr2024	Section of Sample Size Determination included.	N/A	Provided detailed and accurately information about Sample Size Determination.
Section 4.1.1	29Apr2024	Added transition to capsule formulation to be presented as a new disposition	N/A	Required as per study design
Section 4.1.4.1 Definitions and Derivations	29Apr2024	Derived age calculated with Date Of Birth will be used instead of age collected in the eCRF.	N/A	Provided more accurate value for age, adding a decimal position to the age value.
Section 4.1.6.2	29Apr2024	Added presence of non-target PN, overall morbidity type and number of morbidies	N/A	Collected on CRF
Section 4.1.7	29Apr2024	Added last version of dictionaries, updated AstraZeneca Drug Dictionary to WHOdRUG Dictionary	N/A	As per latest coding standards

Section 4.2	29Apr2024	Added clarification that CCI analyses	N/A	Clarification for the CSP analysis expectactions

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
		are not in scope of CSP		
Section 4.4.1.1 and Section 4.2.1.2	29Apr2024	Removed sentence around the interpretability of the primary and supplementary analysis	N/A	Out of scope for SAP
Section 4.2.3	29Apr2024	Detailed information about Derivation and Analysis of Palatability	N/A	Provided detailed and accurately information about Analysis of Palatability.
Section 4.2.5.4 and Section 4.2.5.6	29Apr2024	Updated Table with Overall Visit Response and with BOR categories	N/A	It was not correct
Section 4.2.5.7	29Apr2024	Added that ORR will be presented for the totals and not only by cohort	N/A	It was missing but needed for the data interpretation
Section 4..2.10.4	29Apr2024	Clarification that MMRM has cohort as fixed factor with estimates on the on the cohort-by-scheduled visit interaction and model not run by cohort	N/A	Clarification on modelling
Section 4.3 Pharmacodynamic Endpoint(s)	29Apr2024	PD analysis will not be performed in CSR.	N/A	PD data were not collected.
Section 4.4.1	29Apr2024	Added derivation of dose by BSA normalised (DBN)	N/A	Requested by PK scientist to help data interpretation in CSR
Section 4.4.2.1 Plasma Concentrations Section 4.4.2.2 Plasma parameters	29Apr2024	Remove cohorts and show the table only for the total by BSA.	Yes	Due to the most of the BSA groups within each cohort have less than 3 participants, PK analysis by BSA groups will be only undertaken in the total global.

Section 4.6.1 Exposure and treatment compliance	29Apr2024	Update text for Duration of exposure calculation adding date of DCO. Transition to capsule formulation information will be listed in the exposure listing.	N/A	Provide clarity and consistency in the Duration of exposure calculation. Transition to capsule formulation information will be listed in the exposure listing.
Section 4.6.2 Adverse Event	29Apr2024	Added granule formulation flag to the AEs listings.	Yes	Provided detailed information about the formulation (granule or

CATEGORY Change refers to:	**Date**	**Description of change**	**In line with CSP?**	**Rationale**
		Added table for AESI		capsule) when the AE starts. Provided terms to be mapped as AESI
Section 4.6.12 Physical Examination Including [redacted]	29Apr2024	Remove summary tables for Physical Examination	Yes	Not necessary, data for Physical Examination are available in listings section. Besides any abnormal or significant event will be collected in AEs section.

1 INTRODUCTION

The purpose of this document is to give details for the statistical analysis of study D1346C00004 supporting the CSR. The reader is referred to the CSP and the CRF for details of study conduct and data collection. This SAP is based on Amendment 4 of the CSP (Version 5.0) dated 15 March 2024.

1.1 Study Design

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

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

This study consists of the following periods:

- Screening (up to 28 days)
- Treatment period (25 cycles)
- Long-term safety follow-up (until participants are 5 years old or commence an alternative systemic NF1-PN treatment, whichever is earlier)

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

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

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

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

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

Data from three evaluable participants in Cohort 1 are needed for the dose finding phase.

After completion of at least one cycle (28 days) of dosing in the first 3 evaluable participants, the SRC will review the emerging safety, tolerability, and PK data of the

granule formulation. To ensure that there are 3 evaluable participants in each dose-finding phase, a maximum of 4 participants will be dosed. In the event that participants are classed as non-evaluable for the dose-finding phase, additional participants will be dosed to ensure there is a minimum of 3 evaluable participants (maximum of 4 evaluable participants). Dosing will be paused whilst the SRC assesses the PK and safety data at the end of dosefinding phase in the first 3 evaluable participants.

If the SRC determines that the selumetinib AUC0-12 and safety are within the acceptable criteria, dosing of additional participants into Cohort 1 will continue, and dosing in the dose-finding phase for Cohort 2 will commence.

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

Once the granule formulation dose schema is identified for Cohort 1, dosing in Cohort 2 will commence in order to have 3 evaluable participants in Cohort 2 in the dose-finding phase. After completion of at least one cycle of dosing in the first 3 evaluable participants, the SRC will evaluate the PK, safety, and tolerability of the granule formulation in this dose schema. The same process described for Cohort 1 will be adopted for Cohort 2 in the dosefinding phase. The dose-finding phase will continue to be assessed in this way until the granule formulation dose schema is identified and recommended for Cohort 2.

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

At enrolment, participants must have a BSA within the range of 0.40 to 1.09 m2; once participants attain a BSA between 1.10 and 1.29 m2, they will be encouraged to transition to the capsule formulation, if feasible; however, all participants must remain on the granule formulation until after they have completed their third cycle of treatment. Upon transition to the capsule formulation, PK sampling should be performed on Day 7 (range of Days 4 to 14) as long as the participant has received 3 consecutive days of twice daily dosing with capsule formulation immediately prior to the PK day (see CSP Section 8.5.1.1 for more details).

2 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

3 DATA ANALYSIS CONSIDERATIONS

Summary statistics will be presented as per the AstraZeneca Corporate CSRHLD Reporting Standards to ensure consistency and alignment across AstraZeneca clinical studies.

3.1 Timing of Analyses

There are 3 planned DCOs for this study.

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

2 Safety and efficacy of the granule formulation (DCO2):

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

3 Long term safety follow-up for participants until they reach the age of 5 years or commence an alternative systemic NF1-PN treatment, whichever if the earlier (Final analysis and DCO3):

DCO3 and final analysis will occur when all participants in the study (Global and Japan Cohorts) have had the opportunity to complete their last assessment in the study, including the safety follow-up for participants aged < 5 years. All of the safety/tolerability analyses will be updated with the data captured after DCO2 (safety of the granule formulation).
The different analyses planned for the DCOs are provided in Table 1.

Table 1 Summary of Outcome Variables and Timing of Analyses

Outcome variable	**Timing of analyses**
Study population/demographic data	
Outcome variable	**Timing of analyses**
Disposition	DCO1, DCO2, and DCO3

Analysis sets	DCO1
Demographic characteristics	DCO1
Baseline and disease characteristics	DCO1
Important protocol deviations	DCO1, DCO2, and DCO3
Medical history	DCO1
Prior and concomitant medication	DCO1, DCO2, and DCO3
Efficacy data	
ORR[redacted]	DCO2
Clinical outcome assessment data	
Parent-reported palatability	DCO1 and DCO2
[redacted]	DCO2
[redacted]	DCO2
[redacted]	DCO2
[redacted]	DCO2
Outcome Variable	**Timing of analyses**
[redacted]	DCO2
[redacted]	DCO2
Safety Data	
Exposure and treatment compliance	DCO1, DCO2, and DCO3
Adverse events	DCO1, DCO2, and DCO3
Laboratory measurements	DCO1, DCO2, and DCO3
Vital signs (including height, weight, and BSA)	DCO1, DCO2, and DCO3
ECG and ECHO	DCO1, DCO2, and DCO3
Ophthalmologic assessments	DCO1, DCO2, and DCO3
Knee (or wrist) MRI/X-ray	DCO1, DCO2, and DCO3
Performance status	DCO1, DCO2, and DCO3
Physical examination	DCO1, DCO2, and DCO3
[redacted]	DCO2 and DCO3
PK data	

Selumetinib and N-desmethyl selumetinib plasma concentration data and PK parameters	DCO1 and DCO2
Pharmacodynamic data	
pERK inhibition	DCO1 [a] and DCO2

[a] Only if all Pharmacodynamic data are already available at DCO1. If available at DCO1, Pharmacodynamic data will not be presented at DCO2.

CCI [redacted] CCI ; BSA, body surface area; CCI CCI ; DCO, data cut-off; CCI CCI ; ECG electrocardiogram; ECHO, echocardiogram; CCI [redacted] ; CCI [redacted] ; MRI, magnetic resonance imaging; ORR, objective response rate; PD, pharmacodynamic; CCI , CCI pERK, phosphorylated extracellular signal regulated kinase; CCI ; PK, pharmacokinetic; CCI [redacted] .

3.2 Analysis Populations

3.2.1 Enrolled

All participants who signed the informed consent form (ICF) are considered enrolled.

3.2.2 Pharmacokinetic Analysis Set

All participants who received at least one dose of selumetinib and who have at least one post-dose quantifiable plasma concentration with no IPDs.

IPDs here refer to documented important clinical protocol deviations potentially affecting PK analysis. In order to categorise the important clinical protocol deviations, prior to database lock, a data review meeting will be conducted to assess each participant's evaluability for the PK analysis set. The data review will take into account the IPDs, compliance, AEs, concomitant medications, and PK sample timing and quality, which may have a potential effect on the PK analysis of each datapoint. Any issues thought to impact the PK data may result in the exclusion of impacted concentration data from the PK analysis and/or exclusion of impacted concentrations and parameters from the PK summaries rather than exclusion from the PK analysis set. The reason(s) for exclusion will be documented by the PK Scientist in the Non-compartmental PK Analysis (NCA) Notes and discussed in the CSR.

The available concentration and parameter data for any participants excluded from the PK data summaries will be listed and flagged with the reason for exclusion. The concentration data for participants excluded from the PK summaries will be presented in the individual figures of concentration versus time plots.

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

3.2.3 Safety Analysis Set

All participants who received at least one dose of selumetinib.

3.2.4 Summary of outcome variables and analysis sets

The analysis sets for each outcome variable are provided in Table 2. For some outcome variables, the analysis set will use a further subset (eg, participants who are evaluable for the analysis of CCI are those who CCI [redacted] analysis), which are described in detail in the endpoint analysis sections in Section 4.2.

Table 2 Summary of Outcome Variables and Analysis Sets

Outcome variable	Analysis set
Study population/demographic data	
Disposition	All Enrolled
Demography characteristics	Safety and PK
Baseline and disease characteristics	Safety
Important protocol deviations	Safety
Medical history	Safety
Prior and concomitant medication	Safety
Efficacy data	
CCI [redacted]	Safety
Clinical outcome assessment data	
Parent-reported palatability	Safety
CCI [redacted]	Safety
CCI [redacted]	Safety
CCI [redacted]	Safety
CCI [redacted]	Safety
CCI [redacted]	Safety
CCI [redacted]	Safety
Safety data	
Outcome variable	**Analysis set**
Exposure and treatment compliance	Safety
Adverse events	Safety

Laboratory measurements	Safety
Vital signs (including height, weight, and BSA)	Safety
ECG and ECHO	Safety
Ophthalmologic assessments	Safety
Knee (or wrist) MRI/X-ray	Safety
Performance status	Safety
Physical examination	Safety
CCI CCI	Safety
PK data	
Selumetinib and N-desmethyl selumetinib plasma concentration data and PK parameters	PK
Pharmacodynamic data	
pERK inhibition	Safety

CCI CCI BSA, body surface area; CCI ; CCI, CCI ; ECG, electrocardiogram; ECHO, echocardiogram; CCI , CCI CCI ; MRI, magnetic resonance imaging; ORR, objective response rate; CCI , CCI ; pERK, phosphorylated extracellular signal regulated kinase; CCI PK, pharmacokinetic; CCI

3.3 General Considerations

The below mentioned general principles will be followed throughout the study:

- Descriptive statistics will be used for all variables, as appropriate. Continuous variables will be summarised by the number of observations, mean, standard deviation, minimum, Q1, median, Q3, and maximum. For log-transformed data, it is more appropriate to present geometric mean, geometric coefficient of variation, median, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.
- For continuous data, the minimum and maximum will be displayed with the same accuracy as the original data. For laboratory data where decimal precision is provided, the maximum and minimum will be displayed to the standard decimal precision. The mean, median, Q1, and Q3 will be rounded to one additional decimal place compared to the minimum/maximum. The standard

deviation will be rounded to 2 additional decimal places compared to the minimum/maximum.

- For categorical data, percentages will be rounded to one decimal place with the exception of CCI, which is presented as a whole number. For 0 results, the percentages will not be included, and only 0 will be presented as a result of the categorical variable.
- Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment group.
- Descriptive summaries for all endpoints will be based on the planned visit schedule unless otherwise stated.
- SAS® version 9.4 or above will be used for all analyses.

3.3.1 Baseline and Change from Baseline Definition

Baseline is defined as the last non-missing value obtained prior to the first dose of selumetinib.

Assessments on the day of the first dose where time is not captured will be considered prior to the first dose if such procedures are required by the CSP to be conducted before the first dose.

If two or more measures are recorded on the same day with no time (or on the same day with the same time/timepoint), then the average will be used as the baseline. For nonnumeric laboratory tests (ie, some of the urinalysis parameters) where taking an average is not possible, then the best value would be taken as baseline as this is the most conservative.

In all summaries, the change from baseline variables will be calculated as the posttreatment value -minus the value at baseline.

3.3.2 Study day

Study day is calculated in relation to the date of first dose of study intervention.

- Study Day 1 is defined as the day of first dose of study intervention.
- Study days prior to the date of first dose of study intervention are defined as the date of assessment – date of first dose of study intervention.
- Study days after the first dose of study intervention are defined as: (date of assessment – date of first dose of study intervention) + 1.

3.3.3 On-Treatment MRI

On-treatment MRI data will be defined as MRI data after the date of first dose of study intervention until the study intervention discontinuation date, DCO, or last day of Cycle 25, whichever occurs first.

3.3.4 Visit Window for safety and clinical outcome assessments

Visit windows will be defined for any presentations of safety and COAs that summarise values by visit. The following conventions will be applied:

- The time windows should be exhaustive so that data recorded at any timepoint have the potential to be summarised. Inclusion within the time window should be based on the actual date and not the intended date of the visit.
- All unscheduled visit data should have the potential to be included in the summaries.
- The window for the visits following baseline will be constructed in such a way that the upper limit of the interval falls halfway between the target days of the current and the next scheduled visit (the lower limit of the first post-baseline visit will be Day 2). If an even number of days exists between two consecutive visits, then the upper limit will be taken as the midpoint value minus 1 day. For example, the visit windows for vital signs data (with 2 weeks between scheduled assessments for Cycle 1 and 4 weeks for Cycle 2 onwards) are as follows:

  − Cycle 1 Day 15, visit window Days 2 to 21 −
  Cycle 2 Day 1, visit window Days 22 to 42 −
  Cycle 3 Day 1, visit window Days 43 to 70 −
  Cycle 4 Day 1, visit window Days 71 to 98 −
  etc.
- For summaries showing the maximum or minimum values, the maximum/minimum value recorded on treatment will be used (regardless of where it falls in an interval).
- Listings display all values contributing to a time point for a participant.
- For visit-based summaries, if there is more than one value per participant within a time window, then the closest value to the scheduled visit date will be summarised, or the earlier, in the event that the values are equidistant from the nominal visit date. The listings should highlight the value for the participant who contributed to the summary table, wherever feasible.

Note: In summaries of extreme values, all post-baseline values collected are used including those collected at unscheduled visits regardless of whether or not the value is close to the scheduled visit date.

3.3.5 Handling of Unscheduled Visits

Unscheduled visits are included in the method of assigning data to scheduled visits described in the rules in Section 3.3.4 above. Unscheduled visits are not included as separate visits in the summary tables.

For summaries at the participant level, such as of extreme values, all post-baseline values collected are used to derive a participant-level statistic including those collected at unscheduled visits and regardless of whether they appear in the corresponding visit-based summary.

3.3.6 Missing Data

In general, other than for partial dates, missing data will not be imputed and will be treated as missing unless specifically described in an analysis section. However, safety assessment values of the form of "< x" (ie, below the LLOQ) or "> x" (ie, above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "< x" or "> x" in the listings.

3.3.6.1 Missing Adverse event or concomitant medication dates

For missing AE/concomitant medication start dates, the following will be applied:

- Missing day: Impute the 1st of the month unless the month and year are the same as the month and year of the first dose of study intervention then impute first dose date.
- Missing day and month: Impute 1st of January unless the year is the same as in the first dose date, then impute first dose date.
- Completely missing: Impute the first dose date unless the end date suggests it could have started prior to this, in which case impute the 1st of January of the same year as the end date.

An imputed start date of an AE must be prior to the end date of the AE.

For missing AE/concomitant medication end dates, the following will be applied:

- Missing day: Impute the last day of the month unless the month is the same as the month of the last dose of study intervention then impute last dose date.
- Missing day and month: Impute 31st of December unless the year is the same as in the last dose date then impute last dose date.

- Completely missing: Assume that the AE is still ongoing (ie, do not impute a date). The imputation of dates for AEs and concomitant medications is used to determine if an AE is treatment emergent and whether a medication is concomitant. Flags are retained in the database indicating where any programmatic imputation has been applied, and in such cases, any durations are not calculated. If the imputed end date is after the date of study discontinuation then the end date will instead be taken as the date of study discontinuation

3.3.6.2 Missing dates of diagnosis

For missing dates of diagnosis, if the day and/or month is missing, use 01 and/or Jan. If the year is missing put the complete date to missing.

3.3.6.3 Missing death dates

If a participant is known to have died where only a partial death date is available, then the date of death will be imputed as the latest of the last date known to be alive + 1 from the database and the death date using the available information provided:

- For missing day only: Use the 1st of the month.
- For missing day and month: Use the 1st of January.

The last date known to be alive for each individual participant is defined as the latest date among all start/end/assessments/collection dates unrelated to death.

3.3.6.4 AEs with missing causality

AEs that have missing causality (after data querying) will be assumed to be related to study intervention.

3.3.7 COVID-19 Impact

Summaries of data relating to the impact of the global/country situation will be generated including the following:

- Participant disposition related to the global/country situation
- IPDs related to the global/country situation
- Listing for participants affected by the global/country situation
- Listing for participants with reported issues in the Clinical Trial Management System due to the global/country situation

3.3.8 Multiplicity/Multiple Comparisons

Not applicable.

3.3.9 Participant Disposition for Clinical Outcome Assessments

The cumulative participant disposition at each scheduled assessment where the COAs are collected will summarise the number and percentage of participants with the following:

- COAs expected
- Not expected due to disease progression
- Not expected due to death
- Not expected due to other reasons

A COA is expected as long as the participant is alive and within the first 25 cycles of treatment. Except for the palatability test where if the subject it not on treatment or if the subject transitioned to capsules the COA is not expected.

It should be noted that not all participants are expected to complete each type of questionnaire. Table 3 provides an overview of expected questionnaire completions by age of participant at that assessment.

Table 3 Overview of Eligible Participants Completing Questionnaires by Respondent and Age of Participant

		Age			
Assessment	**Respondent**	CCI	CCI	CCI	CCI
Palatability	Parent/guardian report	Y [a]	Y [a]	Y [a]	Y [a]
CCI	CCI	Y	Y	Y	Y [b]
CCI	CCI				Y [b]
CCI	CCI	Y	Y	Y	Y
CCI	CCI	Y	Y	Y	Y
CCI	CCI	Y			
CCI	CCI		Y	Y	Y
CCI	CCI	Y	Y	Y	Y

[a] Palatability will be assessed for participants receiving granule formulation. If the participant transitions to capsules assessment is not expected anymore.

[b] CCI will be completed by the CCI for participants aged CCI years at the time of study entry (date of signature of consent) or those who, in the opinion of the Investigator, are unable to CCI CCI. The CCI will be used to assess CCI in participants aged CCI years at the time of study entry (date of signature of consent) who are able to CCI.

CCI

3.3.10 Compliance Definition for Clinical Outcome Assessments

Summary measures of compliance over time will be derived for the COAs. These will be based on the following:

- All items/questions completed
- At least meets minimum requirements for calculation of one subscale or a total score of the questionnaire (applicable to CCI only)
- At least meets minimum requirement for calculation of the CCI (applicable to CCI , CCI scale only)
- At least one question completed

For COAs with only one question (CCI), the category "Questionnaire completed" will be presented.

CCI compliance will be summarised for AM and PM of each visit. The participant will have complied if the CCI " field of the diary is not missing.

The compliance for palatability will be summarised by item and week and based on the following:

- Expected number of participants
  - A participant is expected to complete Item 2 only if she/he responded 'No' at least once to Item 1.
  - A participant is expected to complete Item 3 only if she/he responded "No" at least once to Item 1 and or "Other" to Item 2, or having first responded "Yes" to Item 1.
- Expected number of entries
  - The expected number of diary entries for Items 1, 4, and 5 is; expected number of participants x 2 (number of daily assessments) x the number of days the participant is on treatment without transitioning to capsules in the first week of the Cycle 1 or Cycle 7 (until a maximum of 7 days).
  - The expected number of diary entries for Item 2 is: number of entries (Item 1 = "No").

  - The expected number of diary entries for Item 3 is: number of entries (Item 1 = "No" and Item 2 = "Other") plus number of entries (Item 1 = "Yes").

- Subjects with at least on item completed at least once (count and percentage)
  - Percentage will be calculated as the number of participants with item entry completed at least once divided by the expected number of participants in a week.
- Item completion rate (count and percentage)
  - Completion rate will be calculated as the number of actual completed item diary entries divided by the expected number of item diary entries in a cycle.

3.4 Sample Size Determination

Global Cohorts (Cohorts 1 and 2)

Approximately CCI participants will be dosed in Cohorts 1 and 2 to achieve CCI evaluable participants at the recommended granule formulation dose schema, of whom at least CCI participants will be aged ≥ 1 to < 4 years (with at least 3 aged < 2 years) and at least CCI participants will be aged ≥ 4 to < 7 years. A sample size of CCI participants will provide reasonable precision to characterise PK and safety.

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

With a minimum of CCI evaluable participants in each age group and CCI evaluable participants in total, the numbers of participants in the CCI age groups will fall between a combination of CCI to a combination of CCI. With sample sizes of CCI CCI in an age group, the power to show that the CCI CI of the AUC0-12 geometric mean falls within the acceptance range (CCI to CCI-fold of the SPRINT AUC0-12 geometric mean; FDA Guidance 2014) will be 90%, 99.9% and > 99.9%, respectively. The power for two age groups falling within the acceptance range simultaneously will therefore be 90% × 99.9% ≈ 90% and 99.9% × 99.9% ≈ 99.9% for the CCI combination and CCI combination, respectively. This sample size calculation assumes that there is a CCI difference in exposure between the granule and capsule formulation and assumes an inter subject gCV% of CCI (Wang et al 2012). The choice of gCV% is based on observations from Study 89 CCI) and the SPRINT study CCI).

In the dose-finding phase of this study, the exposure AUC0-12 will be monitored on an ongoing basis. The minimum sample size for each cohort and the study may be re estimated

when CCI evaluable participants in that cohort have provided acceptable PK exposures. The re estimation will use the observed inter-subject gCV%. Table 4 below shows the minimum sample sizes required in each age group corresponding to different variability and different scenarios.

Table 4 Sample Size Estimations based on Inter-subject gCV% and Expected Differences in AUC0-12 between SPRINKLE and SPRINT studies.

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

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

Japan Cohort

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

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

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

4 STATISTICAL ANALYSIS

This section provides information on the definitions, derivations, and analysis/data presentation per domain.

Not all analyses will be performed for each DCO. Table 1 provides detailed information on the expected outputs.

For DCO1 and DCO2, all available data will be used for the planned analyses as specified in Table 1. For DCO3, the data of a subset of participants who are aged < 5 years after 25 cycles of selumetinib treatment or discontinuation of study intervention will be presented.

The starting dose schema was approved by the SRC as the recommended dose schema in both cohorts at the end of the dose-finding phase.

The analysis will be presented for the Global Cohorts (Global Cohort 1, Global Cohort 2, and both Global Cohorts combined), the Japan Cohort, and for all participants (all cohorts combined), except for the PK analyses where the Global Cohorts and the Japan Cohort will be presented separately without combining.

4.1 Study Population

The domain "Study Population" covers participant disposition, analysis sets, protocol deviations, demographics, baseline characteristics, medical history and concomitant disease, and prior and concomitant medications and procedures.

Study analysis populations are defined in Section 3.2.

The analysis set used for each analysis is specified in the relevant sections below.

4.1.1 Participant Disposition and Completion Status

4.1.1.1 Presentation

Participant disposition will be summarised, presenting the number of participants enrolled and the number and percentages of participants who did and did not receive treatment, who discontinued study intervention, who transitioned to capsule formulation, who entered the long-term safety follow-up (participants < 5 years of age after 25 cycles or discontinuation of study intervention), and who discontinued the study. A breakdown by reason for participants discontinuing study intervention and discontinuing from the study will be included in this summary. The number of participants ongoing on treatment and in the study at the time of the DCO will also be presented.

Summaries of data relating to the impact of the global/country COVID-19 situation will include the number who discontinued study intervention and withdrew from the study due to the global/country situation and listings for participants affected by the global/country situation.

Listings presenting details of discontinuations by individual participant will be produced for those enrolled participants discontinuing study intervention and discontinuing the study.

Disposition data will be presented for all enrolled participants.

4.1.2 Analysis Sets

4.1.2.1 Definitions and Derivations

The definitions and derivations of the analysis sets are described in Section 3.2.

4.1.2.2 Presentation

The number of participants in each analysis set and the reason for exclusion from each analysis set will be summarised.

A listing of individual participants not included in each analysis set will be provided.

4.1.3 Protocol Deviations

4.1.3.1 Definitions and Derivations

Protocol deviations will be defined as any change, divergence, or departure from the study design in the CSP. Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Protocol deviations and IPDs are defined in the protocol deviation plan and will be finalised at the data review meeting before database lock. IPDs are identified from the complete set of protocol deviations. IPDs are those that may significantly impact the reliability of the study data or that may significantly affect a participant's rights, safety, or wellbeing.

4.1.3.2 Presentation

A summary table will be produced to show the number and percentage of participants with any IPD and by category of IPD.

The individual participant data for IPDs will also be listed.

IPD data will be presented for all participants in the safety analysis set.

4.1.4 Demographics

4.1.4.1 Definitions and Derivations

Date of birth (dd/mm/yyyy) and age are recorded on the CRF. Age at Screening will be calculated using date of birth and the Screening visit date, rounded to 1 decimal place. If Day of date of birth is missing or unknown (NA/mm/yyyy), Day = 1 (first day of the month) will be imputed for Age calculation (01/mm/yyyy).

Age at Screening = [(Screening visit date- date of birth)/365.25]

If Day and Month of birth are both missing or unknown, the Age recorded in the CRF will be used.

Age at Screening will used in the statistical analysis.

4.1.4.2 Presentation

A summary table of demographic data of age, sex, race, ethnicity, and country will be produced, and demographic data will be listed.

Demographic data will be presented for all participants in the safety analysis set.

4.1.5 Baseline Characteristics

4.1.5.1 Definitions and Derivations

Baseline BSA group will be defined as the BSA (m^2) range group used for the granule formulation dose schema for selumetinib:

- ≥ 0.40 to < 0.50 m^2 • ≥ 0.50 to < 0.60 m^2 • ≥ 0.60 to < 0.70 m^2 • ≥ 0.70 to < 0.90 m^2
- ≥ 0.90 to < 1.10 m^2
- ≥ 1.10 to ≤ 1.29 m^2

4.1.5.2 Presentation

Characteristics of height, weight, and BSA (m^2) and BSA group at baseline will be summarised and listed.

Baseline characteristic data will be presented for all participants in the safety analysis set.

4.1.6 Disease Characteristics

4.1.6.1 Definitions and Derivations

Missing diagnostic dates will be imputed for the summary table as described in Section 3.3.6.2.

4.1.6.2 Presentation

A summary table of characteristics of time from diagnosis of NF1 to start of study intervention, time from diagnosis of inoperable PN to start of study intervention, reasons for inoperable PN (eg, PN encasement of vital structures, PN close proximity to vital structures, etc.), and NF1 diagnostic criteria (eg, any cafe-au-lait spots, bilateral freckles in axilla or groin, etc.) will be produced. Presence of non-target PNs, PN location, PN symptoms, PN laterality, PN measurability overall morbidity type and number of morbidies, incomplete coverage, and the reasons for incomplete coverage for both target and non-target PN will be included.

A listing of disease characteristics will be produced for individual participants. Results of any previous genetic testing for NF1 will be included in the listing only.

Disease characteristic data will be presented for all participants in the safety analysis set.

4.1.7 Medical History and Concomitant Disease

4.1.7.1 Definitions and Derivations

Medical and surgical history will be coded using the MedDRA [26.1 version or higher].

Prior PN therapy will be coded using the WHODrug Dictionary [2023.09 version or higher] ATC Classification codes.

Any medical history that is ongoing at the time of informed consent is considered current medical history; otherwise, it will be considered past medical history.

4.1.7.2 Presentation

The number and percentage of participants with prior PN therapy, prior radiotherapy, and surgical history will be summarised. A summary table of prior PN therapy will be produced by ATC code and generic term. A frequency table showing the number of participants with prior radiotherapy by ATC code and generic term will be presented. Summary tables of surgical history and past and current medical history will be produced by system organ class and preferred term.

The individual participant data for medical history (past and current), prior PN therapy, prior radiotherapy, and surgical history will also be listed.

Data will be presented for all participants in the safety analysis set.

4.1.8 Prior and Concomitant Medications and Procedures

4.1.8.1 Definitions and Derivations

Medications received prior to, concomitantly, or post-treatment are coded using the AstraZeneca Drug Dictionary ATC Classification codes.

For the purpose of inclusion in prior and/or concomitant mediation or therapy summaries, incomplete medication start and stop dates are imputed as detailed in Section 3.3.6.1.

Prior, concomitant, and post-treatment medications and procedures are defined based on imputed start and stop dates as follows:

- Prior medications and procedures are those taken prior to study intervention with a stop date prior to the first dose of study intervention.

- Concomitant medications and procedures are those with a stop date on or after the first dose date of study intervention (and could have started prior to or during treatment).
- Post-treatment medications and procedures are those with a start date after the last dose date of study intervention.

Missing coding terms are listed and summarised as "Not coded".

Procedures will be coded using the MedDRA (26.1 version or higher).

4.1.8.2 Presentation

The following summary tables of the number and percentage of participants by ATC code and ATC text will be produced:

- Summary of prior medications
- Summary of allowed concomitant medications
- Summary of disallowed concomitant medications
- Summary of post-treatment medications

All concomitant medications will be listed.

Medication data will be presented for all participants in the safety analysis set. Procedures will not be summarised but will be listed. The individual participant data for subsequent PN therapy will also be listed.

4.1.9 Study Intervention Compliance

This is covered in Section 4.6.1.

4.2 Endpoint Analyses

This section covers details related to the endpoint analyses such as primary, secondary, and other endpoints including sensitivity and supportive analyses.

The CCI [redacted] and CCI [redacted] analyses will not form part of the clinical study report and will not be handled by the statistical and programming vendor. The CCI [redacted] and CCI [redacted] analyses will be analysed and presented separately from the main clinical study report. Thus, they are outside the scope of this SAP.

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
To determine the PK of selumetinib after administration of the selumetinib granule formulation				
Primary	Selumetinib AUC0-12 derived after single dose administration	PK	Descriptive statistics	4.4
To assess the safety and tolerability of the selumetinib granule formulation				
Primary	AEs, AESIs and SAEs. Duration of exposure and treatment compliance percentage. Absolute values and changes from baseline in Laboratory assessments. Vital signs, ECG, ECHO, ophthalmologic assessment, Knee (or wrist) MRI/X ray, and performance status.	Safety	Descriptive statistics	4.6
To assess the palatability of the selumetinib granule formulation				
Secondary	Palatability will be assessed using the parent-reported observer palatability assessment.	Safety	Descriptive statistics	4.2.3
To further assess the PK of selumetinib and N-desmethyl selumetinib metabolite after administration of the selumetinib granule formulation				

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Secondary	Single and multiple dose plasma concentrations and PK parameters of selumetinib and N-desmethyl selumetinib (see Section 4.4 for list of parameters).	PK	Descriptive statistics	4.4
To evaluate the efficacy of the selumetinib granule formulation by assessment of ORR as determined by ICR per REiNS criteria				
Secondary	ORR Safety ORR estimate and	4.2.5	two-sided 95% CI based on the exact CCI [redacted]	

To evaluate the efficacy of the selumetinib granule formulation by assessment of CCI and CCI as determined by ICR per REiNS criteria				
Exploratory	CCI	Participants who have a CCI in safety	CCI CCI CCI CCI	4.2.6
Exploratory	CCI	Safety	CCI	4.2.7
Exploratory	CCI	Safety	CCI CCI	4.2.8
Exploratory	CCI	Participants who have a CCI in safety	CCI	4.2.9
To evaluate the efficacy of the selumetinib granule formulation by assessment of CCI				

Statistical category	Endpoint	Population	Population level summary (analysis)	Details in section
Exploratory	CCI	Safety	Descriptive statistics, estimate LSMeans, and associated 95% CI for MMRM for change from baseline in the CCI	4.2.10
To evaluate the efficacy of the selumetinib granule formulation by assessment of CCI				

Exploratory	CCI	Participants aged < CCI years at the time of study entry (date of signature of consent) or those who, in the opinion of the Investigator, are unable to CCI in safety	Descriptive statistics, estimate LSMeans, and associated 95% CI for MMRM for change from baseline in the weekly average	4.2.11
Exploratory	CCI	Participants aged ≥ CCI years of age at the time of study entry (date of signature of consent) who are able to CCI in safety	Descriptive statistics, estimate LSMeans, and associated 95% CI for MMRM for change from baseline in the weekly average	4.2.12
Exploratory	CCI	Safety	Descriptive statistics	4.2.13
Exploratory	CCI	Safety	Descriptive statistics	4.2.14
Exploratory	CCI	Safety	Descriptive statistics	4.2.15
To evaluate the safety of the selumetinib granule formulation by assessment of CCI				

Statistical category	**Endpoint**	**Population**	**Population level summary (analysis)**	**Details in section**
Exploratory	CCI	Participants aged < CCI years in safety at the time of assessment in safety	Descriptive statistics	4.6.13
Exploratory	CCI	Participants aged ≥ CCI years at the time of assessment in safety	Descriptive statistics	4.6.14

Exploratory	CCI	Participants aged ≥ CCI years at the time of assessment in safety	Descriptive statistics	4.6.15
Exploratory	Physical examination including CCI CCI	Safety	Descriptive statistics	4.6.12
To evaluate the Pharmacodynamic effect of selumetinib in PBMCs				
Exploratory	Change from baseline in Pharmacodynamic markers, which may include, but may not be limited to, pERK inhibition	Participants weighing ≥ 27 kg for pERK in safety	Descriptive statistics	4.3
To determine the PK of selumetinib and N-desmethyl selumetinib after administration of the selumetinib capsule formulation				
Exploratory	Single and multiple dose plasma concentrations and PK parameters of selumetinib and N-desmethyl selumetinib (see Section 4.4 for list of parameters)	PK	Descriptive statistics	4.4

CCI analyses will be completed to investigate the selumetinib exposureresponse relationship for safety, biomarkers and efficacy.				
Statistical category	**Endpoint**	**Population**	**Population level summary (analysis)**	**Details in section**
Exploratory	CCI analyses will be completed to assess the effect of CCI on selumetinib granule and capsule PK, including all paediatric PK data available. In addition, if data allow, CCI CCI analyses will be completed to investigate the selumetinib exposure-response relationship for safety, biomarkers and efficacy.	Not defined in the CSR	Details of the CCI CCI and CCI analyses will be described in the modelling analysis plan finalised before database lock. The CCI and CCI analyses will be presented separately from the main clinical study report.	NA

AE, adverse event; AUC0-12, partial area under the concentration-time curve from time 0 to 12 hours; CCI ; CI, confidence interval; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; CCI , CCI ; CCI , CCI ; ECG, electrocardiogram; ECHO, echocardiogram; CCI CCI ; CCI ; LSMEANS, least square means; MMRM, mixed model repeated measures; MP, metabolite: parent ratio; MRI, magnetic resonance imaging; NA, not applicable; ORR, objective response rate; PBMC, peripheral blood mononuclear cell; CCI , CCI Inventory; pERK, phosphorylated extracellular signal regulated kinase; CCI ; PK, pharmacokinetics: REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis; CCI CCI CCI

4.2.1 Primary Pharmacokinetic Endpoint

The primary PK endpoints are selumetinib AUC0-12 derived after a single dose administration as defined in Section 4.4.

The derivation and analysis of all PK parameters are described in Section 4.4.

4.2.1.1 Primary Analysis of the Primary Endpoint

In the Global Cohorts (Cohorts 1 and 2), the selumetinib AUC0-12 geometric mean and 95% CI (from one sample t-statistic) from single dose administration (Cycle 1 Day 1) will be determined for each age group and total.

4.2.1.2 Supplementary Analyses of the Primary Endpoint

In the Global Cohorts (Cohorts 1 and 2), the selumetinib AUC0-12 geometric mean and CCI CI (from one sample t-statistic) from single dose administration (Cycle 1 Day 1) will be determined for each age group and total.

Further analyses are described in Section 4.4.

4.2.2 Primary Safety Endpoints

Safety endpoints, derivations, and analysis are described in Section 4.6.

4.2.3 Palatability

4.2.3.1 Definition

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

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

A copy of the palatability scale is provided in CSP Appendix J 6. The questions are separated in items as follows:

- Item 1: Did your child take their study medication this morning/evening? (Yes/No)
- Item 2: What was the reason for missing the dose? (Only if Item 1 = No)
- Item 3: Choose the response that best matches a description of what you observe of the child's willingness to swallow the study medication (if Item 1 = Yes or [if Item 1 = No and Item 2 = Other])
- Item 4: Was any behaviour observed when the study medication was given to this child that would be indicative of a negative response to the palatability of the study medication? (If Yes, three additional questions will be answered: 1. Did the child turn their head to reject intake of the medication? 2. Did the child twist their face or mouth in an expression of displeasure? 3. Did the child display any other negative behaviour?)
- Item 5: Were you able to prepare and dose the granules according to the Handling Instructions? (If No, one additional question will be answered: If no, please indicate which area/s you had difficulty in following?)

4.2.3.2 Analysis of Palatability

Summaries for cumulative participant disposition and compliance over time (defined in Sections 3.3.9 and 3.3.10, respectively) by each scheduled visit week will be reported.

Derived Number of expected entries, Counts and percentages of completed entries will be summarised for items 1 to 3. Summaries by Cycle 1 Week 1, by Cycle 7 Week 1 and overall will be presented.

For item 2 besides of all responses, the combination of the responses "My child did not want to take the dose / My child could not swallow the medication (indicating palatability issues)" will be presented. For item 3 besides of all responses, the combination of the responses "Swallowed without problem / some resistance but did swallow" and "Spit out some/all medication / vomited up medication" will be presented.

For Items 1 to 3, the percentage distribution of completed entries over the number of expected entries at Cycle 1 Week 1 and Cycle 7 Week 1 will be visualised using a stacked Bar Chart combining all categories responses in the bar of each item, by summing up to 100%. The plot with be repeated separately for Cycle 1 Week 1 and for Cycle 7 Week 1, and overall.

All results will also be listed.

4.2.4 Secondary Pharmacokinetic Endpoint

The definition, derivation, and analysis of all PK parameters are described in Section 4.4.

4.2.5 Secondary Efficacy Endpoint Objective Response Rate

4.2.5.1 Derivation of REiNS Tumour Response

For all participants, the REiNS tumour response data will be used to determine each participant's visit response according to the REiNS criteria. Tumour assessments will be measured by volumetric MRI. Baseline radiological tumour assessments are to be performed in the 28-day screening period. Unless clinically indicated otherwise, tumour assessments of the target and non-target PN (if relevant) will be obtained at screening and every 4 cycles (16 ± 1 weeks) relative to the date of first dose for the first 13 cycles and subsequently every 6 cycles (24 ± 1 weeks). The MRI data for participants who discontinue selumetinib prior to Cycle 25 will be collected if a suitable MRI is performed as standard of care until the time when they would have completed 25 cycles of treatment or they commence an alternative systemic NF1-PN treatment, whichever is the earliest. Volumetric MRI assessment will be performed by an AstraZeneca-appointed imaging CRO according to the REiNS criteria. A double read of all MRI scans will be performed. The ICR reviewers will be blinded to cohort and dose schema. Further details of the ICR will be documented in the IRC.

All volumetric MRI scans for all participants (including those at unscheduled visits or outside visit windows) will be collected on an ongoing basis and sent to an AstraZeneca-appointed imaging CRO for central analysis. The investigator will select the target PN and non-target PN (if relevant) based on the results of the Screening PN assessments. The details about target PN location and non-target PN location (if relevant) will also be collected and sent to the imaging CRO to ensure that the independent reviewer also follows the most clinically relevant PN. The imaging CRO will determine the tumour measurements of the target PN and non-target PN.

To determine the level of response, the average over the two assessed PN volumes from the double read will be derived, and follow-up scans will be compared to the baseline scan or the scan at the time of best response after documenting a PR for the same PN. Using the REiNS criteria, a change in volume of 20% is used to indicate an increase or decrease of

PN volume. For all participants, the target PN (see Section 4.2.5.2) and non-target PN (see Section 4.2.5.3), if applicable, will be assessed and both given a response (see Table 5 and Table 6), and any new PNs will be recorded. At each visit, participants will be programmatically assigned an overall REiNS visit response of CR, PR, SD, or progressive disease (PD) using the information from target PNs, non-target PNs, and new PNs and depending on the status of their disease compared with baseline and previous assessments (see Table 7). If a participant has a PN assessment that cannot be evaluated, then the participant will be assigned a visit response of NE.

4.2.5.2 Target PN

The target PN is selected at screening. The target PN will be defined as the most clinically relevant PN (signs/symptoms/complications that have the most impact on the participant in the opinion of the Investigator) that is measurable by volumetric MRI analysis. If there is a second PN that is also considered clinically relevant, this may be identified as a non-target PN at baseline; only one non-target PN can be selected. Both target and non-target PNs must be symptomatic, measurable, and inoperable.

The target PN visit response will be derived as per Table 5 using the average over both baseline PN volume assessments and the average over both visit PN volume assessments from ICR. Table 5 is based on the recommendations from Dombi et al 2013.

Table 5 Target PN Visit Responses (REiNS)

Visit responses	Description
Complete response (CR)	Disappearance of the target PN.
Partial response (PR)	Decrease in the volume of the target PN by 20% or more compared to baseline.
Progressive disease (PD)	Increase in the volume of the target PN by 20% or more compared to baseline or the time of best response after documenting a PR.
Stable disease (SD)	Insufficient volume change to qualify for either PR or PD (a < 20% increase or < 20% decrease in the volume of the target PN).
Not evaluable (NE)	Data unavailable for target PN assessment.

PN, plexiform neurofibromas; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

cCR and cPR will be derived as CR/PR achieved on a consecutive scan within 3 to 6 months (± 1 week) with no missed or non-evaluable visits as per assessment schedule.

4.2.5.3 Non-Target PN and New PN

Only one non-target PN may be selected. Non-target PN must also be clinically relevant and measurable by volumetric MRI analysis. The target PN must also be symptomatic,

measurable, and inoperable. This section provides the definitions of the criteria used to determine and record a response for the non-target PN at each MRI assessment.

Non-target response will be derived using the PN volume over both ICR assessments as per Table 6:

Table 6 Non-Target PN Visit Responses (REiNS)

Visit responses	Description
Progressive disease (PD)	Unequivocal progression of an existing non-target PN. 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.
Non-progressive disease (non-PD)	Insufficient volume change to qualify for PD.
Not applicable (NA)	No non-target PN recorded at baseline.
Not evaluable (NE)	Data unavailable for non-target PN assessment.

PN, plexiform neurofibromas; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

Table 6 is based on the recommendations from Dombi et al 2013.

Details of any new PNs will also be recorded in the CRF with the date of the first scan that revealed the new PN(s). The appearance of a new PN (with the exception of new discrete subcutaneous neurofibromas) that is unequivocally and completely distinct and separate from the target PN and the non-target PN, if applicable, or unequivocal progression of an existing non-target PN also qualifies for PD. The new PN must be confirmed by scans with PN details recorded in the CRF. Once a new PN has been identified, at subsequent time points, it will be classified as either absent, present, or NE (in the case where image quality issues prevent a full assessment of the previously identified new PN). For new PNs assessed by ICR, if during the double read both reviewers disagree, a third radiologist will perform adjudication. The assessment of the adjudicator will be used to define the overall visit response as described in the next section. Further details on the adjudication process can be found in the IRC.

4.2.5.4 Overall Visit Response

Table 7 defines how the previously defined target PN and non-target PN visit responses will be combined with new PN information to give an overall visit response.

Table 7 Overall Visit Responses

Target PN	Non-target PN	New PN	Overall visit response
CR	Non-PD or NE or NA	No or NE	CR
PR	Non-PD or NE or NA	No or NE	PR
SD	Non-PD or NE or NA	No or NE	SD
PD	Any	Any	PD
NE	Non-PD or NE or NA	No or NE	NE
Any	Any	Yes	PD
Any	PD	Any	PD

CR, complete response; NA, not applicable; NE, not evaluable; PD, progressive disease; PN, plexiform neurofibroma; PR, partial response; SD, stable disease.

The overall visit response will be derived programmatically based on the derived target PN and non-target PN responses as well as the adjudicated new PN response as described in the previous sections. In addition, the ICR will provide two overall visit responses, one response for each reviewer of the double read. The ICR and investigator visit response will only be listed in source data listings. The handling of CCI in the ICR data can be found in the IRC.

4.2.5.5 Objective Response Rate Definition and Derivations

ORR will be defined as the percentage of participants with measurable disease who have a cCR (defined as disappearance of the target PN, confirmed by a consecutive scan within 3 to 6 months after the first response (± 1 week) with no missed or non-evaluable visits as per assessment schedule, see Section 4.2.5.2) or cPR (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, see Section 4.2.5.2) as determined by ICR per REiNS criteria.

The confirmation by a consecutive scan within 3 to 6 months (± 1 week) will be derived as CR/PR achieved on consecutive visit with no missed or non-evaluable visits as per assessment schedule.

Any cCR or cPR that occurred after a subsequent NF1-PN treatment (following study intervention discontinuation) will not be included in the numerator for the ORR calculation. Participants with no post-baseline MRI assessments will be considered as non-responders (not having a cCR or cPR).

4.2.5.6 Best Objective Response Definition

BOR will be calculated based on the overall visit responses from each MRI assessment as described in Section 4.2.5.4. It is the best response a participant has had following the start of intervention but prior to starting any subsequent NF1-PN therapy and up to and including progression or the last evaluable MRI assessment in the absence of progression. Categorisation of BOR will be based on REiNS using the following response categories: cCR, CR, cPR, PR, SD, PD, and NE.

The different ways of achieving a BOR of cCR, CR, cPR, or PR are shown in Table 8.

Table 8 BOR Categories

Post-baseline visit N	Post-baseline visit N+1	BOR
PR	PR/CR	cPR
PR	SD/PD/NE	Unconfirmed PR
CR	CR	cCR
CR	PR/SD/PD/NE	Unconfirmed CR
PR/SD/NE	CR	Unconfirmed CR
SD/NE	PR	Unconfirmed PR
NE	NE	NE

BOR, best objective response; c Confirmed; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Best objective response will be determined programmatically based on REiNS from the overall visit response using all data up until the first progression event or the last evaluable MRI assessment in the absence of progression. Best objective response will be derived using data whilst on-treatment MRI (see Section 3.3.3). The denominators will be consistent with those used in the ORR analysis.

Participants with no post-baseline MRI assessments will be considered as non-responders. For participants whose progression event is death, BOR will be calculated based on all evaluable MRI assessments prior to death using data whilst on-treatment MRI (see Section 3.3.3).

4.2.5.7 Primary Analysis of the Secondary Endpoint

ORR will be presented with corresponding 2-sided exact 95% CI based on the Clopper Pearson method (Clopper and Pearson 1934) by cohort, total in global, total in Japan and total in study.

ORR will be derived using data whilst on-treatment MRI (see Section 3.3.3).

Data will be summarised and analysed using the safety analysis set.

4.2.5.8 Sensitivity Analyses of the Secondary Endpoint

Not applicable.

4.2.5.9 Supplementary Analyses of the Secondary Endpoint

The following supplementary analyses will be presented as follows:

- Same analyses as described in the above section will be done on data using all MRI scans (regardless of treatment discontinuation but excluding MRI scans after starting subsequent NF1-PN treatment [if applicable]).
- Changes in target PN volume (absolute and percentage change from baseline) over time by cohort and total. The average from the two ICR volume assessments will be used in the analysis as tumour volume. Corresponding box plots will be presented. All PN volume data will be listed, including the two ICR volume and the average.
- BOR will be calculated based on the overall visit responses from each MRI assessment. BOR is the best response a participant has had following the start of intervention but prior to starting any subsequent therapy and up to and including progression or the last evaluable MRI in the absence of progression. BOR will be summarised by cohort and total. BOR and the overall visit response will be listed, including the ICR and investigator visit response.
- Best percentage change from baseline will be derived using the best evaluable on-treatment MRI assessment and will be summarised by cohort and total. A corresponding waterfall plot will be presented.

4.2.6 CCI

4.2.6.1 Definition

For the subset of participants who have a CCI , CCI will be defined as the CCI , as determined by ICR per REiNS criteria.

The CCI should coincide with the CCI endpoint (see Section 4.2.7). The date of the CCI will be defined as the CCI .

4.2.6.2 Derivations and Censoring Rules

If a participant[CCI], then their[CCI] will use the[CCI] Section 4.2.7.2). The derivation formula for[CCI] is[CCI] [CCI] will be derived based on the actual MRI assessment dates and not visit dates.

4.2.6.3 Primary Analysis of[CCI]

A[CCI] of[CCI] by cohort and total will be presented including a[CCI] table.[CCI] will also be calculated using the[CCI] and presented in a summary table by cohort and total. The percentage[CCI] at 4, 8, and 12 months and every 6 months thereafter will be summarised based on the[CCI].

Only participants who have a[CCI] will be included in this analysis.

Swimmer plots that clearly show the profile of each participant who[CCI] by cohort will also be produced. Additional graphical symbols to depict the[CCI], [CCI] will be added. On treatment will be designated with a different colour than post-treatment.

[CCI] will be derived using data whilst on-treatment MRI (see Section 3.3.3). Data will be summarised and analysed using the safety analysis set.

4.2.6.4 Additional Analyses of[CCI]

Same analyses as described in the above section will be done on data using all MRI scans (regardless of treatment discontinuation but excluding MRI scans after starting subsequent NF1-PN treatment [if applicable]).

4.2.7 [CCI]

4.2.7.1 Definition

[CCI] will be defined as the[CCI] (by ICR per REiNS criteria) of[CCI]). [CCI] is defined in Section 4.2.5.2. The[CCI] of existing clinically relevant non-target PN is also considered[CCI] as described in Section 4.2.5.3.

4.2.7.2 Derivations and Censoring Rules

Participants who[CCI] at the time of analysis will be[CCI]. However, if the participant[CCI], the participant will be[CCI]. The details of censoring rules are listed in Table 8.

The derivation formula for CCI is CCI [redacted].

If the participant has no evaluable MRI assessments post-baseline, they will be censored at Cycle 1 Day 1 unless they die within two cycles from baseline. The CCI time will be derived based on actual MRI assessment dates and not visit dates.

Table 9 Summary of Censoring Guidelines for CCI

Assessment	Date of event, Death or Censoring	PFS Outcome
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI
No evaluable MRI assessment or no baseline data and no death within two cycles from baseline	Cycle 1 Day 1	Censored

MRI, magnetic resonance imaging; CCI [redacted].

Based on the scheduled visit assessment scheme (ie, every 4 cycles until Cycle 13 and every 6 cycles from then onwards), the definition of 2 missed MRI assessments will change over time and is calculated as the protocolled time between 2 subsequent scans + the protocol-allowed visit window for an early visit at the previous assessment + the protocolallowed visit window for a late visit at the expected assessment (see Table 10).

Table 10 Two Missed Visits Window Rule

Scheduled assessments	Previous REiNS assessment	Two missed MRI assessments window
Q16w ± 1 week up to Week 48	Up to Week 15 (<Day 106)	33 weeks (231 days)
	Weeks 15 to 31 ≥106 to ≤217	34 weeks (238 days)
	Weeks 31 to 47 ≥218 to ≤329	42 weeks (294 days)
Q 24w ± 1 week	Week 47 ≥330	50 weeks (350 days)

MRI, magnetic resonance imaging; Q16W, every 16 weeks; Q24W, every 24 weeks; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

4.2.7.3 Primary Analysis of CCI

A CCI of CCI will be presented including a CCI table by cohort and total. CCI will also be calculated using the CCI and presented in a summary table by cohort and total. The percentage CCI at 4, 8, and 12 months and every 6 months thereafter will be summarised based on the CCI.

CCI will be derived using data whilst on-treatment MRI (see Section 3.3.3). Data will be summarised and analysed using the safety analysis set.

4.2.7.4 Additional Analyses of CCI

Same analyses as described in the above section will be done on data using all MRI scans (regardless of treatment discontinuation but excluding MRI scans after starting subsequent NF1-PN treatment [if applicable]).

4.2.8 CCI

4.2.8.1 Definition

CCI will be defined as the CCI by ICR per the REiNS criteria.

4.2.8.2 Derivations and Censoring Rules

Participants who CCI at the time of analysis will be censored at their last evaluable MRI assessment. However, if the participant CCI after two or more missed cycles, the participant will be censored at the latest evaluable MRI assessment. Refer to Section 4.2.7.2 for further details on the derivation of two or more missed cycles.

The derivation formula for CCI is CCI.

If the participant has no evaluable MRI assessments post-baseline, they will be censored at Cycle 1 Day 1. The CCI will always be derived based on actual MRI assessment dates and not visit dates.

4.2.8.3 Primary Analysis of CCI

A CCI will be presented including a CCI table by cohort and total. CCI will also be calculated using the CCI and presented in a summary table by cohort and total. The percentage CCI at 4, 8, and 12 months and every 6 months thereafter will be summarised based on the CCI.

CCI will be derived using data whilst on-treatment MRI (see Section 3.3.3). Data will be summarised and analysed using the safety analysis set.

4.2.8.4 Additional Analyses of [redacted]

Same analyses as described in the above section will be done on data using all MRI scans (regardless of treatment discontinuation but excluding MRI scans after starting subsequent NF1-PN treatment [if applicable]).

4.2.9 [redacted]

4.2.9.1 Definition

[redacted] will be defined as the [redacted] (Section 4.2.6).

4.2.9.2 Derivations

The [redacted] will always be derived based on the actual MRI assessment dates and not visit dates.

Only participants who have [redacted] will be evaluated for [redacted].

The derivation formula for [redacted] is [redacted].

4.2.9.3 Primary Analysis of [redacted]

A [redacted] of [redacted] will be presented including a [redacted] table by cohort and total. [redacted] will also be calculated using the [redacted] and presented in a summary table by cohort and total. The percentage [redacted] at 4, 8, and 12 months and every 6 months thereafter will be summarised based on the [redacted].

[redacted] will be derived using data whilst on-treatment MRI (see Section 3.3.3). Data will be summarised and analysed using the safety analysis set.

4.2.9.4 Additional Analyses of [redacted]

Same analyses as described in the above section will be done on data using all MRI scans (regardless of treatment discontinuation but excluding MRI scans after starting subsequent NF1-PN treatment [if applicable]).

4.2.10 [redacted]

4.2.10.1 Definition

[redacted] will be measured using the [redacted]. The [redacted] will be used for participants who are aged [redacted] years at the time of the assessment, and the [redacted] will be used for participants who are aged [redacted] years at the time of the assessment. In this study, [redacted] will be used.

The CCI Scales for participants aged CCI years consist of CCI

The CCI Scales for participants aged CCI years consist of CCI

A copy of the CCI is provided in CSP Appendix J 5. The CCI questionnaire will be performed at visits specified in the CSP.

4.2.10.2 Derivations

Each item is scored on a CCI .

The CCI report items are reverse-scored and linearly transformed to a CCI CCI so that higher scores indicate better CCI . Subscale scores are computed as the sum of the items divided by the number of items answered (this accounts for missing data). A Total Scale Score will also be derived as the sum of all the items divided by the number of items answered on all the scales. If more than 50% of the items in the scale are missing, the scale score is not computed.

The CCI will be further pooled into the CCI :

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

At each post-baseline assessment, the absolute change in CCI scores from baseline will be calculated as the post-baseline value minus baseline value for each item, CCI , CCI .

The change from baseline values in the CCI , CCI , CCI will be classified as improvement/no

change/deterioration compared to baseline scores at each scheduled visit using the CMT reported in the literature (CCI) as follows:

- Improvement: absolute change from baseline ≥ CMT points
- Deterioration: absolute change from baseline ≤ - CMT points
- No change: absolute change from baseline > CMT and < CMT points

between The CMT points differ for the CCI and are relevant only for the CCI . The CMTs are reported in Table 11 based on CCI .

Participants will be classified with impaired global CCI Yes/No at each scheduled visit using the CCI . Participants are classified with impaired global CCI if their scores fall one standard deviation below the population sample mean as reported by CCI ; exact thresholds are reported in Table 11.

Table 11 PedsQL Cut-off Scores (Total Scale, Physical, and Psychosocial) Denoting At-Risk for HRQoL Impairment and Thresholds for Clinically Meaningful Changes for Parent/Guardian-report

CCI scores	Cut-off scores indicating CCI (if values fall below)	Clinically meaningful thresholds
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

CCI .

4.2.10.3 Handling of Missing Data

If more than 50% of the items in the scale are missing, the CCI is not computed. If any of the subscales are missing for the CCI , then it will not be calculated.

4.2.10.4 Analysis of CCI

All analyses of the CCI will be based on the transformed scores only. Summary statistics will be presented by cohort and total.

Summaries for cumulative participant disposition and compliance over time (defined in Section 3.3.9 and 3.3.10, respectively) by each scheduled visit will be reported.

For the CCI

CCI, all age groups can be analysed together. For the CCI, the age groups CCI) can be analysed together, while the CCI for age group CCI years needs to be analysed separately.

CCI

A summary table with descriptive statistics for the absolute values and change from baseline in the CCI will be presented for each scheduled visit by age group (CCI.

CCI

A summary table with descriptive statistics for the absolute values and change from baseline in the CCI will be presented for each scheduled visit.

Mean absolute values and change from baseline in theCCI will be plotted over time.

Counts and percentages for impaired global CCI in the CCI will be provided for each scheduled visit.

Counts and percentages for category improvement/no change/deterioration for CCI, CCI at each scheduled visit will be provided.

Change from baseline in the CCI will be analysed using a REML-based MMRM analysis. The analysis will be based on observed data (ie, data collected at each time point without carrying forward previous values). As drop out will accumulate during the study, the proportion of available data may become too small for adequately estimating the statistical model. Therefore, the first visit where less than CCI participants have non-missing data will be used as a cut-off point, and only visits prior to that time point will be included in the model.

The response variable will be the change from baseline to each post-baseline scheduled visit. The model will include terms for scheduled visit, baseline CCI score, cohort, cohort-by-scheduled visit interaction, and baseline-by-scheduled visit interaction. The model will present least square mean estimates estimated on the cohort-by-scheduled visit interaction, standard errors, 95% CIs, and p-values for mean changes from baseline to each scheduled visit.

The analysis will be conducted using PROC MIXED in SAS. Missing data will be modelled through direct likelihood techniques, which use the information from the observed data via the within-patient correlation structure (covariance matrix) to provide

information about the unobserved outcomes. An unstructured covariance matrix will be used to model the within-patient correlations between the repeated measurements.

If the fit of the unstructured covariance structure fails to converge, every attempt should be made to ensure convergence is obtained from the unstructured correlation structure. Parameters will be tried to be estimated by means of the Fisher's scoring algorithm rather than the default Newton-Raphson algorithm. If convergence is still not reached after the change in estimation algorithm, a more parsimonious model will be implemented using one of the following structured covariance structures in order until convergence is reached: first-order autoregressive and compound symmetry. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The unique participant identifier will also be included as a class variable. A REPEATED statement over the visits will be included with the unique participant identifier as the SUBJECT variable in the REPEATED statement.

All CCI data (both the raw and transformed scores) will be fully listed, including individual items, CCI and change from baseline.

Data will be summarised and analysed using the safety analysis set.

4.2.11 CCI

4.2.11.1 Definition

The CCI is an CCI measurement used to assess CCI or for older individuals who are CCI .

The total scale is scored from CCI The scale has CCI , and each is assigned a score of CCI . In this study, the CCI scale will be completed by the CCI at the time of study entry (date of signature of consent) or those who, in the opinion of the Investigator, are CCI .

A copy of the CCI questionnaire is provided in CSP Appendix J 1. The CCI questionnaire will be completed daily in the evening for 7 days after the visits specified in the CSP.

4.2.11.2 Derivations

For each scheduled visit, the weekly average scores will be derived for each item and total score. At each scheduled visit, the CCI questionnaire needs to be completed at least 4

times over 7 days for all [redacted]; otherwise, the weekly average score will not be computed.

The change from baseline values for the weekly average total scale and item scores will be classified according to following categories:

- Worsened [redacted] points compared to baseline
- Worsened [redacted] points compared to baseline
- Worsened [redacted] point compared to baseline
- Stable [redacted]
- Improved [redacted] point compared to baseline
- Improved [redacted] points compared to baseline
- Improved [redacted] points compared to baseline

For the individual items, the categories Worsened [redacted] points and Improved [redacted] points are not applicable.

The post-baseline changes in the total score will be classified as improvement/no change/deterioration compared to baseline scores at each scheduled visit using the CMT reported in the literature ([redacted]) as follows:

- Improvement: absolute change from baseline [redacted] points
- Deterioration: absolute change from baseline [redacted] points
- No change: absolute change from baseline [redacted] points

[redacted]

[redacted] will be based on two related components: [redacted].

Two definitions for the [redacted] will be considered.

The primary definition will include only participants with a [redacted] weekly average score [redacted] points at baseline and will be defined as a decrease of [redacted] points in score without an increase in [redacted] (eg, increase of at least 1 category in the [redacted] category [moving from a score of 0 to a score of 1], see below for definition).

A secondary definition of [redacted] will be considered to also include the asymptomatic participants as follows:

- For participants with CCI weekly average score CCI points at baseline, CCI will be defined as a decrease of CCI points in score without an increase in the CCI score; OR
- For participants with a CCI weekly average score CCI points AND an CCI score CCI points at baseline, CCI will be defined as stable (or reduced) CCI score compared to baseline AND a decrease of at least 1 level in the CCI category.

CCI

Information on all CCI by participants in CCI will be collected on the CCI as well as on the CCI A modified CCI CCI will be used to quantify and score CCI in the study by the AZ clinical team. The additional class of 2 is added to include typical CCI used by NF1-PN participants.

For this study, the following categories in Table 12 will be used in the analysis:

CCI	CCI	
CCI	CCI	CCI
CCI	CCI	
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI
CCI	CCI	CCI

CCI

An increase of 1 point or more compared to baseline (represents an increase to a CCI CCI) is defined as an increase in the CCI score.

CCI within 7 days from the first questionnaire CCI completion date will be considered to assess CCI . If a participant CCI of a different score within the same period the higher score precedes, for example, if a participant CCI of score 1 and one of score 3, score 3 will be considered for the relevant period.

4.2.11.3 Analysis of CCI

Summaries for cumulative participant disposition and compliance over time (defined in Section 3.3.9 and 3.3.10, respectively) by each scheduled visit will be reported. Summary statistics will be presented by cohort and total.

A summary table with descriptive statistics for the absolute values and change from baseline in the weekly average total score will be presented for each scheduled visit.

Counts and percentages for each change from baseline category for the weekly average total score at each scheduled visit will be provided.

Counts and percentages for category improvement/no change/deterioration for the weekly average total score at each scheduled visit will be provided.

Change from baseline in the weekly average total scores will be analysed using a REML-based MMRM (as described in Section 4.2.10.4). usingWithin each cohort, the corresponding baseline value rather than baseline CCI score will be used.

Counts and percentages for CCI at each scheduled visit will be provided.

All CCI data will be fully listed, including individual items, total scores, and weekly averages.

Data will be summarised and analysed using the safety analysis set.

4.2.12 CCI

4.2.12.1 Definition

The CCI is a CCI measure of CCI . In this study, the CCI will be used to assess CCI in children aged CCI years at the time of study entry (date of signature of consent) CCI daily in the evening according to the schedule specified in the CSP. CCI are presented to the child, who will then CCI and give a score.

A copy of the CCI questionnaire is provided in CSP Appendix J 2. The CCI questionnaire will be completed daily in the evening for 7 days prior to each visit specified in the CSP.

4.2.12.2 Derivation

For each scheduled visit, the weekly average score will be derived. At each scheduled visit, theCCI questionnaire needs to be completed at least 4 times over 7 days; otherwise, the weekly average score will not be computed.

The change from baseline values will be classified according to following categories:

- Worsened CCI points compared to baseline
- Worsened CCI points compared to baseline
- Worsened CCI points compared to baseline
- Stable
- Improved CCI points compared to baseline
- Improved CCI points compared to baseline
- Improved CCI points compared to baseline

The post-baseline changes in the weekly average total scores will be classified as improvement/no change/deterioration compared to baseline scores at each scheduled visit using the CMT reported in the literature (CCI) as follows:

- Improvement: absolute change from baseline CCI points
- Deterioration: absolute change from baseline CCI points
- No change: absolute change from baseline CCI points

CCI

The derivation of the CCI is the same as described in Section 4.2.11.2 with the use of the CCI score instead of the CCI score.

4.2.12.3 Analysis of CCI

Summaries for cumulative participant disposition and compliance over time (defined in Section 3.3.9 and 3.3.10, respectively) by each scheduled visit will be reported. Summary statistics will be presented by cohort and total.

A summary table with descriptive statistics for the absolute values and change from baseline in the weekly average total score will be presented for each scheduled visit.

Counts and percentages for each change from baseline category for the weekly average total score at each scheduled visit will be provided.

Counts and percentages for category improvement/no change/deterioration for the weekly average total score at each scheduled visit will be provided.

Change from baseline in the weekly averages will be analysed using a REML-based MMRM (as described in Section 4.2.10.4), and considering CCI score at baseline tather than baseline CCI score.

Counts and percentages for CCI at each scheduled visit will be provided.

All CCI data will be fully listed, including individual scores and change from baseline.

Data will be summarised and analysed using the safety analysis set.

4.2.13 CCI

4.2.13.1 Definition

The CCI instrument is a CCI measure used to assess CCI

A copy of the CCI questionnaire is provided in CSP Appendix J 3. The CCI questionnaire will be performed at visits specified in the CSP.

4.2.13.2 Analysis of CCI

Summaries for cumulative participant disposition and compliance over time (defined in Section 3.3.9 and 3.3.10, respectively) by each scheduled visit will be reported. Summary statistics will be presented by cohort and total.

Counts and percentages for each response option at each scheduled visit will be provided along with the corresponding bar chart.

All CCI data will be listed.

Data will be summarised and analysed using the safety analysis set.

4.2.14 CCI

4.2.14.1 Definition

The CCI is a CCI measure used to CCI CCI

A copy of the CCI questionnaire is provided in CSP Appendix J4. The CCI questionnaire will be performed at visits specified in the CSP.

4.2.14.2 Derivation

The change from baseline values will be classified according to the following categories:

- Worsened CCI compared to baseline
- Worsened CCI compared to baseline
- Worsened CCI compared to baseline
- No change
- Improved CCI compared to baseline
- Improved CCI compared to baseline
- Improved CCI compared to baseline

4.2.14.3 Analysis of CCI

Summaries for cumulative participant disposition and compliance over time (defined in Section 3.3.9 and 3.3.10, respectively) by each scheduled visit will be reported. Summary statistics will be presented by cohort and total.

A summary table with descriptive statistics for the absolute values and change from baseline will be presented for each scheduled visit.

Counts and percentages for each response option at each scheduled visit will be provided along with a corresponding bar chart.

Counts and percentages for each change from baseline category at each scheduled visit will be provided.

All CCI data will be listed.

Data will be summarised and analysed using the safety analysis set.

4.2.15 CCI

4.2.15.1 Definition

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

4.2.15.2 Analysis of the CCI

Descriptive statistics for the CCI at each scheduled visit will be provided, CCI .
Summary statistics will be presented by cohort and total.

All CCI data will be listed.

Data will be summarised and analysed using the safety analysis set.

4.3 Pharmacodynamic Endpoint(s)

This section covers details related to pharmacodynamic endpoints and analyses.

4.3.1 Analysis

Where possible, optional blood samples for exploratory analysis of pharmacodynamic biomarkers in PBMCs can be taken during Cycle 1 Day 1. This analysis includes, but may not be limited to, pERK inhibition. This would require additional blood volume on a PK profile day in addition to the volume required for PK samples and safety samples.

In line with the European Condition requirement that blood volume should not exceed 1% of the total blood volume at any single time, the samples for pERK can only be collected in participants ≥ 27 kg. For a participant who is 6 years old, this would mean that they would have to be approaching the 98th percentile on the UK-WHO growth chart (UK WHO Growth Chart). It is therefore considered these samples would be collected only in the oldest and largest of children.

4.3.2 Sampling schedule

Samples will be taken pre-dose within 10 minutes prior to dosing, at 1 and 3 hours post-dose (± 15 minutes), and at 18 to 24 hours post-dose as described in the CSP Table 16.

4.3.3 Presentation

Not applicable, at the moment to write the current SAP version, with all subjects included. Cycle 1 Week 1 PD data have not been collected and no analysis will be reported.

4.4 Pharmacokinetics

4.4.1 Calculation or Derivation of Pharmacokinetic Parameters

The plasma PK parameters for selumetinib and N-desmethyl selumetinib will be derived using non compartmental methods CCI CCI

The PK parameters will be derived CCI .

PK analysis will be carried out, where data allow, using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations.

Where data allow, the following single-dose PK parameters (Table 13) for selumetinib and N-desmethyl selumetinib will be derived from Cycle 1 Day 1 plasma concentrations.

Table 13 Single-Dose Pharmacokinetic Parameters

PK parameter	Description
Cmax	Maximum observed concentration
tmax	Time to reach the maximum observed concentration
AUC0-6	Partial area under the concentration-time curve from time 0 to 6 hours
AUC0-12	Partial area under the concentration-time curve from time 0 to 12 hours
AUC0-24	Partial area under the concentration-time curve from time 0 to 24 hours
AUClast	Area under the concentration-time curve from 0 to the last quantifiable concentration
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (selumetinib only)
Vz/F	Volume of distribution (apparent) based on the terminal phase following extravascular administration (selumetinib only)
t½λz	Half-life associated with the terminal slope of the concentration-time curve
MPAUC0-6	Metabolite:parent ratio based on AUC0-6
MPAUC0-12	Metabolite:parent ratio based on AUC0-12
MPAUC0-24	Metabolite:parent ratio based on AUC0-24
MPCmax	Metabolite:parent ratio based on Cmax

In addition, where data allow, the following multiple-dose PK parameters (Table 14) for selumetinib and N-desmethyl selumetinib will be derived from CCI CCI

Table 14 Multiple-Dose Pharmacokinetic Parameters

PK parameter	Description
Cmax	Maximum observed concentration
tmax	Time to reach the maximum observed concentration
AUC0-6	Partial area under the concentration-time curve from time 0 to 6 hours
AUC0-12	Partial area under the concentration-time curve from time 0 to 12 hours

AUClast	Area under the concentration-time curve from 0 to the last quantifiable concentration
CL/F	Apparent total body clearance of drug from plasma after extravascular administration (selumetinib only)
Vss/F	Volume of distribution (apparent) at steady state following extravascular administration (selumetinib only)
MPAUC0-6	Metabolite:parent ratio based on AUC0-6
MPAUC0-12	Metabolite:parent ratio based on AUC0-12
MPCmax	Metabolite:parent ratio based on Cmax
RacAUC0-12	Accumulation ratio for AUC0-12
RacCmax	Accumulation ratio for Cmax

The diagnostic PK parameters in Table 15 will be provided, where appropriate.

Table 15 Diagnostic PK parameters

PK parameter	Description
λz	Terminal elimination rate constant
λz upper	Lower (earlier) time used for λz determination
λz lower	Upper (later) time used for λz determination
λzN	Number of data points used for λz determination
Rsq adj	Statistical measure of fit for the regression used for λz determination, adjusted for the number of used data points
λz span ratio	Time period over which λz was determined as a ratio of t½λz
tlast	Time of last observed (quantifiable) concentration.
AUCextr (%)	Extrapolated area under the curve from tlast to infinity
t½λz	Half-life associated with the terminal slope of the concentration-time curve

PK, pharmacokinetic.

In addition, for the PK profiles collected on CCI [redacted] 2 CCI [redacted] BSA normalised (BN) PK parameters and dose normalised (DN) PK parameters for AUC0-6, AUC0-12, AUClast, and Cmax will be derived by programming in SAS for all analytes by dividing the relevant parameters by the

participant's BSA value or the actual administered dose in milligrams (mg), respectively, on the corresponding PK visit.

In addition, dose by BSA normalised (DBN) AUC0-6, AUC0-12, AUClast, and Cmax will be derived by programming in SAS for all analytes by dividing the relevant parameters by the participant's actual administered dose in mg/m^2 on the corresponding PK visit. For the participants who transition to capsule formulation, the ratio of granule:capsule formulation will be determined by programming in SAS for each of these BN and DN parameters.

Additional PK parameters may be determined, where appropriate.

If an entire concentration-time profile is not quantifiable, the profile will be excluded from the PK analysis.

The minimum requirement for the calculation of AUC values will be the inclusion of at least
3 consecutive quantifiable concentrations. Where there are only 3 quantifiable concentrations, at least one of these should follow the peak concentration.

The same analysis as described in Section 4.2.1.1 and Section 4.2.1.2 for the primary endpoint will be performed for N-desmethyl selumetinib.

Details of CCI and CCI analyses will be described in a separate PK modelling analysis plan, which will be finalized before the database lock and is not in scope of this SAP.

4.4.2 Presentation of Pharmacokinetic Data

The plasma selumetinib and N-desmethyl selumetinib concentrations and the PK parameters will be listed and presented in tabular and graphical form, as appropriate, according to the CCI , which include applicable descriptive statistics, defined handling of individual concentrations below the LLOQ, and precision/rounding rules for concentrations and PK parameter data.

Exclusion of concentration and/or parameter data from PK summaries may apply; this will be flagged in the listings with the reason(s) for exclusion.

4.4.2.1 Plasma Concentrations

Selumetinib and N-desmethyl selumetinib plasma concentrations for each scheduled time point will be summarised using appropriate descriptive statistics based on the PK Analysis Set. The summary tables will be presented as follows:

CCI By analyte, BSA group, and PK serial sampling day (CCI

CCI [redacted]

CCI By cohort (Cohort 1, Cohort 2, total global and Japan cohort), analyte, and PK serial sampling day CCI [redacted]

The PK concentrations for the Japan Cohort will be summarised CCI [redacted].

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarised for each dose. Less than three observations > LLOQ are presented as a minimum and maximum with the other summary statistics as NC.

The on-treatment BSA group will be used to present plasma concentrations by BSA group (ie, the BSA group the participant falls within at the relevant scheduled PK sample timepoint from Cycle 1 through Cycle 25). The on-treatment BSA group categories are the same as those defined for the baseline BSA group (see Section 4.1.5.1).

A listing of concentration versus scheduled time data will be presented by cohort, analyte, BSA group, and PK serial sampling day for the PK Analysis Set. A listing of all concentration-time data (ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations) will be presented for the safety analysis set.

Trough concentrations collected at pre-dose on Day 1 of Cycle 5, 13, and 25 will be listed only.

4.4.2.2 Pharmacokinetic Parameters

Individual PK parameters for selumetinib and N-desmethyl selumetinib will be listed and summarised based on the PK Analysis Set. The summary tables will be presented as follows:

- By analyte, BSA group, and PK Day for the total global cohort
- By cohort (Cohort 1, Cohort 2, total global and Japan cohort), analyte and PK Day

The PK parameters for the Japan Cohort will be summarised CCI [redacted]

The ratio granule: capsule formulation for dose normalised parameters will be listed and summarised separately, based on the PK Analysis Set. The summary tables will be presented:

- By analyte, BSA group, and PK Day for the total global cohort
- By cohort (Cohort 1, Cohort 2, total global and Japan cohort), analyte and PK Day

Three observations (> LLOQ if Cmax) are required as a minimum for a PK parameter to be summarised for each dose. Less than three observations (> LLOQ if Cmax) will be presented as a minimum and maximum with the other summary statistics as NC.

The on-treatment BSA group will be used to present plasma concentrations by BSA group (ie the BSA group the participant falls within at the relevant scheduled PK sample timepoint from Cycle 1 through to Cycle 25). The on-treatment BSA group categories are the same as those defined for the baseline BSA group (see Section 4.1.5.1).

4.4.2.3 Graphical Presentation

Individual concentration-time data will be graphically presented on linear and semilogarithmic scales for the PK Analysis Set. Each individual's plot will include the concentration versus actual time profiles from CCI [redacted].

Combined individual concentration versus actual time profiles will be plotted on both the linear and semi-logarithmic scale with all participants overlaid, based on the PK Analysis Set. The combined individual concentrations plots will be separated as follows:

- By analyte, BSA group and PK serial sampling day CCI [redacted] after transitioning to capsule dosing) for the total global cohort
- By analyte, cohort (Cohort 1, Cohort 2, total global and Japan cohort), and PK serial sampling day (CCI [redacted] after transitioning to capsule dosing)

CCI [redacted]

Figures for the geometric mean concentration-time data will be presented on both a linear with (*/gSD) error bars and a semi-logarithmic scale (no error bars), separately for CCI [redacted] after transitioning to capsule dosing, based on the PK Analysis Set. Two group of figures will be presented, with the following variables overlaid on the same plot:

- Analyte, BSA group for the total global cohort
- Analyte and cohort (Cohort 1, Cohort 2, total global and Japan cohort)

CCI [redacted]

In addition, geometric mean concentration-time data will be presented on both a linear with (*/gSD) error bars and a semi-logarithmic scale (no error bars) for the Japan Cohort with the Global Cohorts overlaid on the same plot with different symbols for each cohort, based on the PK Analysis Set, if data permits. The figures will be separated as follows:

- By analyte and PK serial sampling day (CCI after transitioning to capsule dosing)

The on-treatment BSA group will be used to present plasma concentrations by BSA group (ie, the BSA group the participant falls within at the relevant scheduled PK sample timepoint from Cycle 1 through Cycle 25). The on-treatment BSA group categories are the same as those defined for the baseline BSA group (see Section 4.1.5.1).

For box and whisker plots of the PK parameters selumetinib and N-desmethyl selumetinib Cmax and AUC0-12 versus cohort (Global and Japan), the BSA group will be plotted separately by parameter and by CCI after transitioning to capsule dosing for the total global cohort.

Scatter figures with age (years) on the x-axis and PK parameter on the y-axis will be presented to evaluate the effect of age on PK, based on the PK Analysis Set. These scatter figures will be shown for the following:

- Selumetinib single-dose Cmax, AUC0-6, AUC0-12, AUC0-24, AUClast, and tmax
- N-desmethyl selumetinib single-dose Cmax, AUC0-6, AUC0-12, AUClast, AUC024, and tmax
- Selumetinib multiple-dose Cmax, tmax, AUC0-6, AUC0-12, and AUClast
- N-desmethyl selumetinib multiple-dose Cmax, tmax, AUC0-6, AUC0-12, and AUClast

The scatter figures will only be presented for the Global Cohort and will include the geometric mean for Cohort 1, Cohort 2, and Total in Global.

All individual and summary PK figures will be presented separately by analyte.

4.5 Immunogenicity

Not applicable.

4.6 Safety Analyses

The domain "Safety" covers exposure, treatment compliance, AEs, clinical laboratory, vital signs, ECG, ECHO, ophthalmologic examinations, Knee/Wrist MRI/X-ray, performance status, CCI tests.

Safety data will be presented for all participants in the safety analysis set.

All planned data, including off-treatment data for participants who entered the long-term safety follow-up (participants < 5 years of age after 25 cycles of treatment or when they terminate treatment with selumetinib), will be presented in the listings for those assessments specified in the CSP Table 3.

Off-treatment data for participants who entered the long-term safety follow-up (participants < 5 years of age after 25 cycles of treatment or when they terminate treatment with selumetinib) will be presented separately in the summary tables and figures (if not otherwise specified) for those assessments specified in the CSP Table 3.

Off-treatment data will be included up until the first visit after the participant is ≥ 5 years of age or they commence an alternative systemic NF1-PN targeted treatment, whichever is earlier.

4.6.1 Exposure and treatment compliance

4.6.1.1 Definitions and Derivations

Duration of exposure will be defined as follows:

- Duration of exposure = last dose date where dose > 0 mg– first dose date + 1 (if last dose date is missing the earliest date between DCO, date of death and treatment discontinuation date will be used).
- Actual duration of exposure = duration of exposure – total duration of dose interruptions, where duration of exposure will be calculated as above, and a dose interruption is defined as any days with dose = 0 mg and half days if planned frequency is twice per day, but actual frequency is once daily only

This calculation will use the individual start and stop dates and the study intervention dosing frequency on the EX form of the CRF, which will account for any dose interruptions. The actual duration of exposure calculation makes no adjustment for any dose reductions that may have occurred.

<u>Participants who permanently discontinue during a dose interruption</u>

If a participant permanently discontinues study intervention during a dose interruption, then the date of last administration of study medication will be used in the calculation of exposure. In this case, the interruption would not be included in the summary tables, but it will be included in the listings.

Relative dose intensity

RDI is the percentage of the actual dose delivered relative to the intended dose through to study intervention discontinuation. RDI will be defined as follows:

- RDI = 100% * d/D, where d is the actual cumulative dose delivered up to the actual last day of dosing and D is the intended cumulative dose up to the day of treatment discontinuation or actual last day of dosing. D is the total dose that would be delivered if the participant received the planned dose as per the CRF.

Intended cumulative dose is calculated by summing all the individual doses that should have been taken up to and including the last day of treatment according to the protocolplanned dose and schedule. This is defined as follows:

Integer part (rounded up) of [(minimum (date of last dose date where dose >0, date of death, date of DCO) – first dose date + 1) × intended dose according to the protocol] / 0.5
The intended dose of selumetinib is [redacted] mg/m^2 twice daily.

Actual cumulative dose will be calculated by summing all the individual doses the participant actually took up to and including the last day of treatment. This is defined by:

Sum of [((end date of study drug administration – start date of study drug administration + 1) x dose) / 0.5] for each cycle of drug administration recorded on the study drug exposure form up to the minimum of [date of last dose date where dose > 0, date of death, date of DCO].

Treatment compliance

Treatment compliance is the percentage of the actual cumulative dose taken relative to the intended cumulative dose according to the protocol, including the protocol-allowable dose reductions / dose interruptions up to and including the last day of treatment.

4.6.1.2 Presentation

Duration of exposure, actual duration of exposure, RDI, and treatment compliance will be summarised using descriptive statistics for continuous data and listed. Counts and percentages for the number of planned starting dose received, dose interruptions, reasons

for dose interruptions, dose reductions, reason for dose reductions, dose modifications (ie, dose interruption and/or dose reduction), and treatment compliance thresholds will be provided.

Treatment compliance percentage will be summarised as a continuous variable using descriptive statistics and by counts and percentages using the following categories:

CCI

CCI

CCI

Exposure and treatment compliance data will be presented by cohort and total.

Exposure data will be listed, including the date of first exposure to treatment, duration (intended) of exposure (days), actual duration of exposure (days), RDI, treatment compliance, and transition to capsule formulation.

4.6.2 Adverse Events

4.6.2.1 Definitions and Derivations

The MedDRA version 26.1 or higher is used to code AEs. AEs are graded according to the CTCAE version 5.0.

AEs will be collected from the time of signature of the ICF until 30 days after the last dose of selumetinib or 25 cycles of treatment, whichever is earlier. For participants taking part in the long-term safety follow-up (participants < 5 years of age), after 25 cycles of treatment or end of treatment, AEs causally related to selumetinib will be collected until they complete the study in accordance with CSP Table 3. The long-term safety follow-up is designed to assess the long-term safety of selumetinib treatment in participants who are < 3 years of age when they commence selumetinib, as there are no long-term safety data currently available for patients who received selumetinib at this age. No AEs will be collected for participants who are > 5 years of age who remain in the study after 25 cycles of treatment.

A treatment-emergent AE will be defined as an AE that starts, or worsens, after the first dose of selumetinib up to and including 30 days after the last dose of selumetinib.

<u>AEs of special interest</u>

Some clinical concepts (including some selected individual preferred terms and higher-level terms) have been considered AESIs to the selumetinib program.

The AESIs in Table 16 have been identified as a list of categories by the patient safety team.

Table 16 AEs of special interest

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

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

Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgement, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered OAEs and reported as such in the CSR.

A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs. Examples of these could be marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

4.6.2.2 Presentation

Summary tables of the number and percentage of participants with AEs by system organ class and preferred term will be produced for below categories. The number and percentage of participants with AESIs will be summarised by AESI grouped term and preferred term. An overall summary table will include the number and percentage of participants in each category.

- All AEs
- AEs possibly related to study intervention
- AEs of CTCAE grade 3 or higher
- AEs with CTCAE grade 3 or higher, possibly related to study intervention
- SAEs with an outcome of death
- SAEs with outcome of death possibly related to intervention
- All SAEs
- SAEs possibly related to study intervention
- AEs leading to discontinuation of study intervention
- AEs leading to discontinuation of study intervention, possibly related to study intervention
- AEs leading to dose interruption and reduction (separately)
- AESIs
- OAEs

The number of subjects and events will also be presented for non-serious AEs occurring in more than 5% of participants.

CTCAE grades and summaries of the number and percentage of participants will be provided by system organ class, preferred term and maximum reported CTCAE grade.

All AEs, SAEs, AESIs, AEs with outcome of death, AEs leading to treatment discontinuation, and AEs occurring > 30 days after last dose of selumetinib will be listed in the same subject listing.

All AEs listings will include the formulation (granule or capsule) variable at the event start date of the event.

4.6.3 Clinical Laboratory, Blood Sample

4.6.3.1 Definitions and Derivations

Blood samples for the determination of clinical chemistry and haematology will be taken at the visits indicated in the CSP.

The rules described in Sections 3.3.1, 3.3.4, 3.3.5, and 3.3.6 of this document considering the definition of baseline, visit windows, handling of multiple records and records above or below the limit of quantification are followed.

Absolute values are compared to the reference range and classified as low (below range), normal (within range or limits of range), and high (above range). Local reference ranges are used for the primary interpretation of laboratory data.

Changes from baseline in clinical chemistry and haematology will be calculated for each post-dose visit, including the safety follow-up visit for participants who are off treatment.

All laboratory results will be converted to standard units, and CTCAE grades (version 5.0) will be derived at each visit according to the CTCAE grade criteria. For parameters where CTCAE grades are defined and some parameters may have both high- and low-range values, CTCAE grades will be calculated for each set of high and low values. Laboratory parameters that will be summarised, along with details of whether the maximum and/or minimum are of interest and the availability of CTCAE grading are given in Table 17.

Table 17 Haematology and clinical chemistry parameters - Minimum/Maximum of interest

Laboratory Assessment	Maximum of interest	Minimum of interest	CTCAE grading available
Albumin		Yes	Yes
Alkaline phosphatase	Yes		Yes
Alanine aminotransferase	Yes		Yes
Aspartate aminotransferase	Yes		Yes
Total calcium	Yes	Yes	No
Creatinine	Yes		Yes
Gamma-glutamyl transferase	Yes		Yes
Magnesium	Yes	Yes	Yes
Phosphate	Yes	Yes	No
Potassium	Yes	Yes	Yes
Sodium	Yes	Yes	Yes
Total Protein		Yes	No

Total bilirubin	Yes		Yes
Blood urea nitrogen	Yes		No
Creatine kinase	Yes		Yes
Amylase	Yes		Yes
Haemoglobin	Yes	Yes	Yes
Platelets		Yes	Yes
Leukocytes (absolute)	Yes	Yes	Yes
Neutrophils (absolute)		Yes	Yes
Lymphocytes (absolute)	Yes	Yes	Yes
Total red blood cell count		Yes	No

CTCAE, Common Terminology Criteria for Adverse Events.

For parameters with no CTCAE grading that are listed in the Table 17, any on-treatment increase/decrease and TELC are derived. An on-treatment increase is defined as an increase to a value above the upper local laboratory reference limit at any time on treatment for participants with a value below the upper local laboratory reference limit at baseline. An ontreatment decrease is defined as a decrease to any value below the lower local laboratory reference range limit at any time on treatment for participants with a value above the lower local laboratory reference limit at baseline. A TELC is defined as any on-treatment increase or decrease from baseline.

4.6.3.2 Presentations

Haematology and clinical chemistry data will be summarised by scheduled visit using descriptive statistics over time in terms of absolute values and changes from baseline.

Shift tables showing CTCAE grade changes from baseline to worst CTCAE grade on treatment will be produced for parameters with available CTCAE grades (see Table 17). For specific parameters, separate shift tables indicating the hyper- and hypo-directionality of change are produced (see Table 17 parameters with “Yes” for maximum of interest, “Yes” for minimum of interest, and “Yes” for CTCAE grading available). Percentages are based on the number of participants with a baseline value and an on-treatment value.

For parameters in Table 17 with no CTCAE grading (“No” for CTCAE grading available), the number and percentage of participants with any on-treatment increase from baseline, any on treatment decrease from baseline, and a TELC are summarised. Percentages for an increase from baseline are based on the number of participants with a baseline value below

the upper local laboratory reference limit and an on-treatment value. Percentages for a decrease from baseline are based on the number of participants with a baseline value above the lower local laboratory reference limit and an on-treatment value. Percentages for a TELC are based on the number of participants with a baseline value and an on-treatment value.

Haematology and clinical chemistry data in Table 17 will also be presented graphically using boxplots for absolute values and changes from baseline by scheduled visit.

A listing will be provided for participants with potential Hy's law (ALT or AST ≥3× the ULN and total bilirubin ≥2× ULN), where the onset date of ALT or AST elevation is prior to or on the date of total bilirubin elevation.

Laboratory data for the variables displayed in the CSP Table 13 will be listed. Site reference ranges will also be listed. Flags (H or L) will be applied to values falling outside reference ranges (which will be explicitly noted on these listings where applicable) and for the CTCAE grade for parameters for which CTCAE grading applies.

Pregnancy data will also be listed.

4.6.4 Clinical Laboratory, Urinalysis

4.6.4.1 Definitions and Derivations

Urine samples for the determination of urinalysis are collected as described in the CSP.

The rules described in Sections 3.3.1, 3.3.4, 3.3.5, and 3.3.6 of this document considering the definition of baseline, visit windows, how to handle multiple records and records above or below the limit of quantification are followed.

4.6.4.2 Presentations

Urinalysis data will only be listed, and no summary tables will be produced. Site reference ranges will also be listed. Flags (H or L) will be applied to values falling outside reference ranges (which will be explicitly noted on these listings where applicable) and to values for which CTCAE grading applies.

4.6.5 Other Laboratory Evaluations

4.6.5.1 Definitions and Derivations

Not applicable.

4.6.5.2 Presentations

Not applicable.

4.6.6 Vital Signs

4.6.6.1 Definitions and Derivations

Vital signs will be assessed at the timelines specified in the CSP.

The rules described in Sections 3.3.1, 3.3.4, and 3.3.5 of this document considering the definition of baseline, visit windows, and how to handle multiple records are followed.

4.6.6.2 Presentation

All vital signs (temperature, systolic and diastolic blood pressure, pulse rate, respiratory rate, and oxygen saturation) and growth parameters (height, weight, and BSA) will be summarised using descriptive statistics over time in terms of absolute values and change from baseline by scheduled visit.

Vital sign data will be presented graphically using boxplots for absolute values and changes from baseline by scheduled visit.

Individual BSA will be plotted against the study day. Historical measurements of weight and height will be presented on the x-axis as negative study days. Off-treatment data for participants who entered the long-term safety follow-up (participants < 5 years of age after 25 cycles of treatment or when they terminate treatment with selumetinib) will be included in the figure but presented with different symbols.

All vital sign, including BSA group, data will be listed.

4.6.7 Electrocardiogram

4.6.7.1 Definitions and Derivations

The 12-lead ECGs will be recorded at visits specified in the CSP using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Participants that were enrolled on CSP Version 1 (therefore with QTcB as an exclusion criterion at screening) should have both QTcB and QTcF collected at all timepoints throughout the study, and QTcF should be retrospectively calculated and reported for all visits that have previously occurred.

The rules described in Sections 3.3.1, 3.3.4, and 3.3.5 considering the definition of baseline, visit windows, and how to handle multiple records are followed.

The overall evaluation of an ECG is “normal,” “borderline,” or “abnormal,” with abnormalities categorised as either “clinically significant” or “not clinically significant.

4.6.7.2 Presentations

A summary table of absolute values and change from baseline will be presented for each scheduled visit.

A frequency table showing the number of participants with their interpretation of the ECG reading (normal; borderline; abnormal, clinically not significant; abnormal, clinically significant) for each scheduled visit will be presented.

All ECG data will be listed, including a description of the abnormalities.

4.6.8 Echocardiogram

4.6.8.1 Definitions and Derivations

An ECHO to assess LVEF, end diastolic, and end systolic left ventricular volumes will be performed at visits specified in the CSP.

The rules described in Sections 3.3.1, 3.3.4, and 3.3.5 considering the definition of baseline, visit windows, and how to handle multiple records are followed.

4.6.8.2 Presentations

A summary table of absolute values and change from baseline of LVEF, end diastolic, and end systolic left ventricular volumes will be presented for each scheduled visit.

For ejection fraction decrease, a shift table showing CTCAE grades from baseline to maximum on-treatment will be produced.

All ECHO data will be listed.

4.6.9 Ophthalmologic Examinations

4.6.9.1 Definitions and Derivations

An ophthalmologic examination (best corrected visual acuity, intraocular pressure, and slit-lamp fundoscopy) will be evaluated at the times outlined in the CSP and as clinically indicated whilst the participant is on study intervention.

The rules described in Sections 3.3.1, 3.3.5, and 3.3.6 of this document considering definition of baseline, visit windows, and how to handle multiple records are followed.

4.6.9.2 Presentations

A frequency table showing the number of participants with their ophthalmologic examination results (Fundoscopy performed: Yes, No; Type of fundoscopy performed: Indirect, Slit lamp; Indirect and Slit lamp result: normal, abnormal, clinically not significant; or abnormal, clinically significant) by eye (left/right) for each scheduled visit will be presented.

Intraocular pressure will be presented graphically using box plots for absolute values and changes from baseline for each scheduled visit – one box plot for each eye.

Ophthalmology examination data will also be listed for participants, including a description of the abnormalities and relevant baseline result.

4.6.10 Knee/Wrist MRI/X-ray

4.6.10.1 Definitions and Derivations

An MRI/X-ray of the knee will be performed at screening as specified, and if clinically indicated, to monitor growth plates for any signs of physeal dysplasia. The imaging modality that is used at baseline (MRI/X-ray) must be used at all follow-up visits throughout the study. A wrist MRI/X-ray is acceptable if it is not possible to perform knee MRI/X-ray.

4.6.10.2 Presentations

A frequency table showing the number of participants with their diagnosis of the Knee/Wrist MRI/X-ray (normal, abnormal, clinically not significant; or abnormal, clinically significant) for each scheduled visit will be presented.

All Knee/Wrist MRI data will be listed, including a description of the abnormalities.

4.6.11 Performance status

4.6.11.1 Definitions and Derivations

Performance status will be measured as indicated in the CSP. The Lansky performance scale will be used. The scale has a score range of 10 to 100, with 10 being the worst score and 100 being the best. The scale is described in more detail in CSP Appendix H.

The rules described in Sections 3.3.1, 3.3.5, and 3.3.6 of this document considering definition of baseline, visit windows, and how to handle multiple records are followed.

4.6.11.2 Presentations

Shift tables showing score changes from baseline to worst score on treatment will be produced. The performance status score will be listed along with a text description of the score as described in Appendix H of the CSP.

4.6.12 Physical Examination Including CCI

4.6.12.1 Definitions and Derivations

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

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

Physical examination will be performed at time points as specified in the CSP.

4.6.12.2 Presentations

All physical examination data will be listed; descriptive tables will not be produced for physical examination.

4.6.13 CCI

4.6.13.1 Definitions

The CCI is one of the most reliable and widely used tests for CCI . The CCI is derived from the CCI and is a brief measure of CCI , CCI . It is used to identify CCI

The screening test consists of CCI , which are as follows:

CCI
CCI
CCI
CCI

- CCI

All subtests will be administered. A total raw score for each administered subtest is calculated, and then an age-dependent cut score for each subtest is determined CCI :

CCI
CCI

CCI

The CCI at the time of the assessment will be evaluated and collected with this screening test. The CCI will be performed at visits specified in the CSP.

4.6.13.2 Derivations

CCI will be derived from the raw score according to the manual.

4.6.13.3 Presentations

For participants starting with CCI at a later timepoint, data collected after the switch will not be compared.

The frequency count of the CCI will be summarised by scheduled visit for each of the following subtests: CCI

A shift table will be produced to display the CCI shift from the baseline to each post-baseline scheduled visit by subtests.

All results of the CCI will be listed.

4.6.14 CCI

4.6.14.1 Definitions

The CCI consists of CCI
CCI
CCI
CCI
CCI
CCI

The CCI . In the context of this study, CCI will be collected. In Table 18, the CCI are listed, as well as the CCI derived from the subtests as described below.

Table 18 CCI

CCI	
CCI	CCI
CCI	

CCI	CCI
CCI	
CCI	CCI
CCI	
	CCI
CCI	
CCI	
CCI	CCI
CCI	
CCI	CCI
CCI	
CCI	
CCI	
CCI	
CCI	
CCI	
CCI	CCI
CCI	CCI
CCI	
CCI	CCI
CCI	
CCI	CCI

CCI	CCI
CCI	CCI
CCI	
CCI	CCI
CCI	
CCI	
CCI	
CCI	
CCI	
CCI	
CCI	

Both CCI include CCI . The CCI are used to compute the CCI (Table 18). Each of the CCI is calculated based on CCI . The CCI contribute to calculate CCI .

CCI

CCI

CCI

CCI

CCI

The CCI

CCI CCI

CCI

CCI

CCI

CCI

CCI are collected for the CCI, which are converted to CCI, and those are then used to calculate the CCI as well as CCI. Similarly, CCI are also collected for the CCI, which are converted to CCI, and those are then used to calculate the CCI scores.

Standard scores are available for CCI, and those will be collected and analysed. Standard scores have a mean of CCI and a standard deviation of CCI. For subtests, CCI will be analysed. CCI have a mean of CCI and a standard deviation of CCI.

The following classification table can be used to aid the interpretation of standard scores (Table 19):

Table 19 Standard Scores Interpretation

Standard score	Performance
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI

The CCI of participants aged CCI years at the time of the assessment will be evaluated with CCI CCI. The CCI will be performed at visits specified in the CSP.

4.6.14.2 Derivations

For participants with CCI prior to first dose of selumetinib baseline is defined as described in Section 3.3.1. Otherwise, baseline is defined as the first non-missing value of CCI .

Deterioration will be defined for each participant with baseline and post-baseline CCI assessments as change from baseline CCI in the standard scores for the CCI , as well as for the CCI . Change from baseline CCI in the standard scores will be classified as "no deterioration".

4.6.14.3 Presentations

A summary table with descriptive statistics for the absolute values and change from baseline in the standard score of the CCI , as applicable, and CCI , for each scheduled visit will be presented. In addition, descriptive statistics will be provided for the absolute values and change from baseline in the CCI of the CCI listed in Table 16 for each scheduled visit.

Counts and percentages for deterioration/no deterioration at each post-baseline scheduled visit will be provided.

All results of the CCI will be listed.

In addition, the deterioration information for CCI and CCI will be combined in one listing over time. No comparisons between information from different instruments will be performed.

4.6.15 CCI

4.6.15.1 Definitions

The CCI , currently in its CCI edition, is a widely used test of CCI . TheCCI is a standardized tests which consists of a CCI optional supplemental standardized tests are also available, CCI . The CCI and its supplemental tests provide one of the most valid and economical CCI for preschool to adult ages. In the context of this study, only the CCI test is required, and there is no requirement to perform the optional supplemental tests.

Based on the scoring manual CCI , either CCI . If CCI .CCI ,

CCI

Raw scores are obtained for each of CCI CCI, and can then be converted to standard, scaled, percentiles, and other scaling scores using conversion tables from the Appendices B and C of the instrument's manual.

The use of standard scores is strongly recommended; thus, those will be collected and analysed for CCI and the two supplemental tests, CCI. Standard scores have a mean of CCI and a standard deviation of CCI

The visual CCI of participants aged CCI years at the time of the assessment will be evaluated with CCI, CCI The CCI will be performed at visits specified in the CSP.

4.6.15.2 Derivations

For participants with CCI assessments prior to the first dose of selumetinib, baseline is defined as described in Section 3.3.1. Otherwise, baseline is defined as the first non-missing value of CCI. For each of the administered scores, deterioration will be defined for each participant with baseline and post-baseline assessments as change from baseline CCI Change from baseline CCI in the standard scores will be classified as "no deterioration".

4.6.15.3 Presentations

A summary table with descriptive statistics for the absolute values and change from baseline in the standard score of CCI for each scheduled visit will be provided.

Counts and percentages for deterioration/no deterioration at each post-baseline scheduled visit for each test will be provided.

All results of CCI, CCI, CCI will be listed.

In addition, the deterioration information for CCI and CCI will be combined in one listing over time. No comparisons between information from different instruments will be performed.

5 INTERIM ANALYSIS

There is no interim analysis planned for this study.

6 REFERENCES

CCI

CCI

CCI

CCI

CCI

Clopper and Pearson 1934
Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934; 26(4):404-13.

CCI

Dombi et al 2013
Dombi E, Ardern-Holmes SL, Babovic-Vuksanovic D, Barker FG, Connor S, Evans DG, et al. Recommendations for imaging tumor response in neurofibromatosis clinical trials. REiNS International Collaboration Neurology. Nov 2013; 81 (21 supplement 1):33-40.

CCI

CCI

CCI

CCI [redacted]

UK WHO Growth Chart
https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years

CCI [redacted]

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: d1346c00004-sap-ed-3		
Document Title:	Statistical Analysis Plan Edition 3	
Document ID:		
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
	Anna Rigazio	Content Approval
	Ramon Dosantos	Author Approval

Notes: (1) Document details as stored in EVR, an AstraZeneca document management system.

Signature Page for VV-RIM-02718416 v5.0

Approve: Document Level Task Verdict: Approved	PPD Content Approval 02-May-2024 18:56:29 GMT+0000

Approve: Document Level Task Verdict: Approved	PPD Content Approval 02-May-2024 20:19:09 GMT+0000

Signature Page for VV-RIM-02718416 v5.0