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STATISTICAL ANALYSIS PLAN

A PHASE II, RANDOMIZED, OPEN-LABEL STUDY TO ASSESS THE EFFICACY, SAFETY, AND PHARMACOKINETICS (PK) OF MAINTENANCE CABOZANTINIB (XL184) PLUS BEST SUPPORTIVE CARE (BSC) VERSUS BSC IN CHILDREN, ADOLESCENTS AND YOUNG ADULTS (AYA) WITH UNRESECTABLE RESIDUAL OSTEOSARCOMA EITHER AT DIAGNOSIS OR AT FIRST RELAPSE AFTER STANDARD TREATMENT

CLIN-60000-461

This statistical analysis plan (SAP) is based on:
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APPROVAL PAGE

STUDY NUMBER:	CLIN-60000-461
PROTOCOL TITLE:	A phase II, randomized, open-label study to assess the efficacy, safety, and pharmacokinetics (PK) of maintenance cabozantinib (XL184) plus best supportive care (BSC) versus BSC in children, adolescents and young adults (AYA) with unresectable residual osteosarcoma either at diagnosis or at first relapse after standard treatment.
SAP VERSION:	Version 1.0
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The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan:

Name	Company	Function	Date	Signature
PPD	PPD	PPD		eSignature
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	IPSEN			eSignature

HISTORY OF CHANGES

Version Number	Date	Description/Rational for change
1.0	30JAN2026	New document.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABBREVIATION	Wording Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ATC	Anatomical Therapeutic Chemical
AYA	Adolescents and Young Adults
BIRC	Blinded Independent Radiology Committee
BMI	Body Mass Index
BSA	Body Surface Area
BSC	Best Supportive Care
BSCM	Best Supportive Care Medication
BSCR	Best Supportive Care Radiotherapy
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
C1W1D1	Cycle 1 Week 1 Day 1
DCR	Disease Control Rate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EOSI	End of Study Intervention
ETM	Events to Monitor
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
Gy	Gray
HR	Hazard Ratio

ABBREVIATION	Wording Definition
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IRT	Interactive Response Technology
ITT	Intent-to-treat
IWRS	Interactive Web Response System
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MSTS	Musculoskeletal Tumor Society
ORR	Objective Response Rate
OS	Overall Survival
PARR	Planned Analysis Review Report
PCSA	Potentially Clinically Significant Abnormalities
PD	Progressive Disease
PDAP	Protocol Deviation Assessment Plan
PedsQL	Pediatric Quality of Life Inventory
PFS	Progression-free Survival
PK	Pharmacokinetic
PPES	Palmar-plantar Erythrodysaesthesia Syndrome
PR	Partial Response
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient-Reported Outcome
PT	Preferred Term
QD	Once Daily
QoL	Quality of Life
QT	QT interval
QTcF	Corrected QT interval calculated by the Fredericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
RPLS	Reversible Posterior Leukoencephalopathy Syndrome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System®

ABBREVIATION	Wording Definition
SD	Stable Disease
SDS	Standard Deviation Score
SDTM	Study Data Tabulation Model
SE	Standard Error
SI	International System of Units
SMQ	Standardized MedDRA Query
SOC	System Organ Class
StD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures and Listings
TKI	Tyrosine Kinase Inhibitor
TRAE	Treatment-Related TEAE
VAS	Visual Assessment Scale
VEGF	Vascular Endothelial Growth Factor

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses to be completed to support the completion of the Clinical Study Report (CSR) for Clinical Study Protocol (CSP) CLIN-60000-461. It describes the rules and conventions to be used in the analysis and presentation of data, the data to be summarized and analyzed, including specificities of the statistical analyses to be performed.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP will be clearly identified in the respective CSR.

The SAP is to be finalized prior to interim futility analysis. A separate document will be provided for table, figure and listing (TFLs) shells.

Any deviations from the SAP after database lock will be documented in the CSR (Section 9.8 "Changes in the conduct of the study or planned analyses" as per International Council for Harmonisation [ICH] E3).

This analysis plan does not cover pharmacokinetic (PK) and exposure-response analyses.

Planned analyses per CSP will not be performed due to the decision to terminate the study early. Limited summaries will be provided for the abbreviated CSR due to the early termination decision.

The data cutoff date for analyses has been chosen as 25th November 2025, which is the date the study early termination decision was announced to the sites. However, available data up to database lock will be included in the relevant listings.

2 PROTOCOL OVERVIEW

2.1 Study Objectives and Hypotheses

The primary objective of the study is to assess the efficacy of maintenance cabozantinib plus best supportive care (BSC) versus BSC in improving the Progression-free Survival (PFS) in participants with osteosarcoma. The primary analysis for this study will be the comparison of the distribution of PFS as assessed by the Blinded Independent Radiology Committee (BIRC) using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in the intent-to-treat (ITT) population. Assuming proportional hazard for PFS, the hypothesis to be tested for PFS Hazard Ratio (HR) is as follows:

Null hypothesis: HR(cabozantinib plus BSC vs. BSC) ≥1 vs. Alternative hypothesis: HR <1.

The primary, secondary and exploratory endpoints of this study are shown in Table 2-1 below.

Table 2-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of maintenance cabozantinib plus BSC versus BSC in	• PFS by BIRC using RECIST version 1.1. *PFS is defined as the time from the date of randomization to the date of first documented*

Objectives	Endpoints
improving the PFS in participants with osteosarcoma.	*disease progression (according to RECIST version 1.1) or the date of death due to any cause, whichever occurs first.*
Secondary	
• To assess the efficacy of maintenance cabozantinib plus BSC versus BSC in improving PFS rate at 4 months and 1 year, objective response rate (ORR) and disease control rate (DCR).	• PFS rate at 4 months and 1 year by BIRC using RECIST version 1.1. • ORR by BIRC. *ORR is defined as the proportion of participants who have achieved CR or PR determined by BIRC using RECIST version 1.1.* • DCR by BIRC. *DCR is defined as the proportion of participants who have achieved CR, PR, or SD determined by BIRC per RECIST version 1.1.* • PFS, PFS rate at 4 months and 1 year, ORR and DCR as assessed by investigator using RECIST version 1.1.
• To compare overall survival (OS) of maintenance cabozantinib plus BSC versus BSC.	• OS. • OS at 1 year. *OS is defined as the time from date of randomization to the date of death, from any cause.*
• To assess the safety and tolerability of maintenance cabozantinib plus BSC in children and adolescents and young adults (AYA).	• Safety and tolerability of cabozantinib including treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). • Adverse events of special interest (AESIs; events-to-monitor (ETMs)), including growth plate thickening.
• To evaluate the PK of cabozantinib in children and AYA and explore exposure/response relationship with efficacy and safety endpoints, if applicable.	• To characterize the PK of cabozantinib in children and AYA, the inter-individual variability, and to identify the covariates which potentially impact the PK of cabozantinib. • PK parameters, exposure-response relationship between selected PK measures of exposure and safety and efficacy endpoints, if applicable.
• To assess the acceptability and palatability of cabozantinib tablets in children and adolescents.	• Acceptability and palatability in children and adolescents will be assessed using a horizontal visual assessment scale.
• To compare the quality-of-life (QoL) with maintenance cabozantinib plus BSC versus BSC in children and AYA.	• Change from baseline in score for all Pediatric QoL Inventory (PedsQL) Scales including Generic Core Scales and Cancer Modules. • For adults: Change from baseline in European Organisation for the Research and Treatment of

Objectives	Endpoints
	Cancer Quality of Life Questionnaire (EORTC QLQ-C30).
Exploratory	
• To explore pharmacodynamic parameters associated with treatment in blood and potential predictive biomarkers of clinical response to maintenance cabozantinib in blood and/or tissue where feasible.	• Correlation of plasma proteins at baseline or plasma protein changes during treatment with clinical outcomes from maintenance cabozantinib initiation. • Correlation of genomic alterations and/or circulating tumor DNA (ctDNA) concentration at baseline or changes during study intervention and at disease progression where applicable, with clinical outcomes. • Correlation of genomic alternations and/or protein expression in tumor tissue at baseline, with clinical outcomes from maintenance cabozantinib initiation.
• Impact of maintenance cabozantinib in participants experiencing surgery or any other therapy with curative intent.	• Responses after surgery or any other therapy with curative intent and safety profile.

2.2 Overall Study Design and Investigational Plan

This is a phase II, multicenter, randomized, open-label, two-arm, parallel-group study evaluating maintenance cabozantinib plus BSC versus BSC in children and AYA with unresectable residual osteosarcoma, who achieved partial response (PR) or stable disease (SD) at the end of conventional chemotherapy, either in first line diagnosis or after first relapse treated with chemotherapy. Participants who have not received previous chemotherapy at the time of first relapse (who achieved surgical remission, or who were completely resected) are eligible at the time of the subsequent relapse if treated with chemotherapy. The last dose of chemotherapy must have been received at least 4 weeks, but not more than 2 months, before randomization.

Participants will be randomly assigned (1:1) to receive one of the following two study interventions:

- Arm A: Cabozantinib + BSC
- Arm B: BSC alone

Randomization will be stratified according to the setting of the disease at screening: either at initial diagnosis or first relapse after chemotherapy.

The starting dose of cabozantinib for this trial will be 40 mg/m^2/day for children and adolescents (<18 years of age). Cabozantinib will be administered orally once daily (QD) on a continuous dosing schedule for cycles of 28 days, commencing on Cycle 1 Week 1 Day 1 (C1W1D1). Dosing will be performed based on body surface area (BSA) and rounded to the nearest 20 mg using the dosing nomogram (see Appendix 10.8 of the CSP). The cumulative weekly dose of cabozantinib cannot exceed 420 mg.

The starting dose for participants ≥18 years of age will be 60 mg/day.

Rules for dose modifications are outlined in Section 6.6 of the CSP.

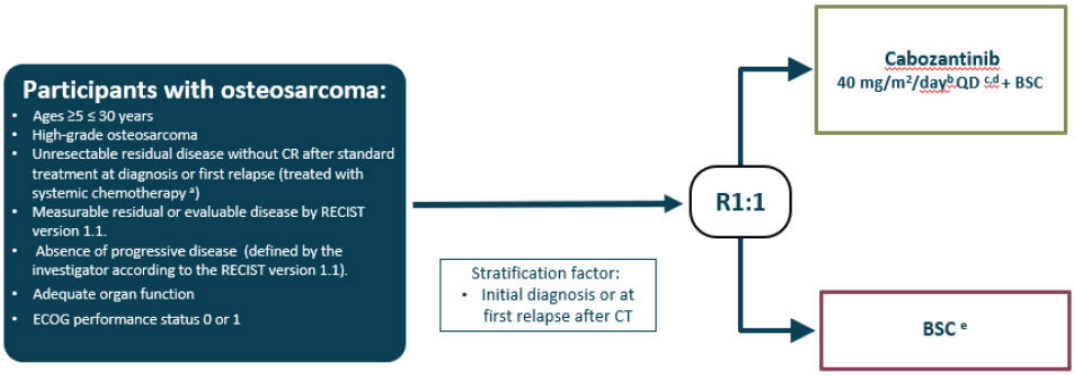
BSC will be administered in both arms per investigator's discretion and institutional guidelines. Per European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/205/95 Rev. 6), BSC includes antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc., but does not include tumor specific therapy.

Tumor disease evaluation will occur every 8 weeks (±7 days) from the date of randomization regardless of treatment delays until there is evidence of progressive disease (PD). Following evidence of PD as per RECIST v1.1 and investigator judgment, participants in the BSC alone arm may switch to receive cabozantinib plus BSC.

Additional criteria for switching include: no new systemic anticancer medication prior to switch, all safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, and that the study is ongoing.

The end of study intervention (EOSI) visit will occur 30 days (±7 days) after the last dose of Investigational Medicinal Product (IMP). During the follow-up period, participants will be contacted every 3 months (±14 days) until whichever of the following occurs first: death, participant request to discontinue from follow-up, or until the last participant to enter survival follow-up period has been followed for 1 year, or the Sponsor decides to discontinue collection of these data in the study. The estimated duration of study for participants including follow-up is at least 24 months or until disease progression or death or unacceptable toxicity. The study schema is shown in Figure 2-1 below.

Figure 2-1: Study Schema



BSC=best supportive care, CR=complete remission, CT=chemotherapy, ECOG=Eastern Cooperative Oncology Group, QD=daily, R=randomization, RECIST=response evaluation criteria in solid tumors

a Receipt of chemotherapy at least 4 weeks, but not more than 2 months before randomization.

b Cabozantinib 40 mg/m^2/day will be given up to a maximum dose of 420 mg/week.

c Cabozantinib will be given on a continuous dosing schedule until disease progression or unacceptable toxicity. A cycle is 28 days.

d Adult participants (≥18 years) will receive cabozantinib at a starting dose of 60 mg.

e BSC excludes non-protocol anticancer therapy. Participants in BSC arm are allowed to switch to cabozantinib arm at disease progression. BSC includes antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy according with the timelines), etc. but does not include tumor specific therapy.

2.3 Sample Size Determination and Power

CCI

[redacted]

2.4 Randomization and Blinding

Participants will be randomly assigned (1:1) to receive either cabozantinib plus BSC or BSC alone.

Randomization will be stratified according to the setting of the disease at screening – either initial diagnosis or at first relapse after chemotherapy.

This is an open-label study - there is no blinding. The protocol states that although this is an open-label study, the study team will be blinded to the randomized treatment assignment by the Interactive Web Response System (IWRS). However, because this is open-label, individual treatment assignments are available through IWRS and Electronic Data Capture (EDC).

Additionally, blinded image reviewers are also blinded to treatment assignments to mitigate bias in determining disease response.

Randomized participants who terminate their study participation for any reason before their first intervention will retain their randomization number (i.e., this number will not be reused). The next participant will be assigned another randomization number, even if he/she should receive the same intervention. Participants who leave the study early will not be replaced.

The Sponsor's randomization manager will keep the master randomization list. A copy of this list will also be provided to the Service Provider in charge of IWRS. The master list and the copy supplied to the service provider in charge of IWRS will be kept confidential in a secure location. Access to the randomization list must remain restricted until authorization is granted to release it for all planned analyses, including the final analysis.

2.5 Schedule of Assessments

The schedule of assessments is presented in Section 1.3 of the CSP.

3 PLANNED ANALYSES

3.1 Data Monitoring

An Independent Data Monitoring Committee (IDMC) will be established to monitor the safety of the study on a regular basis. In addition, the IDMC will also review the interim analysis for PFS. The membership and decision process of the IDMC are independent of the Sponsor and the study clinical investigators.

Unblinded safety data will be reviewed by the IDMC on a periodic basis. Depending on the actual enrollment, the safety review may be initiated 6 months after the first participant is

randomized and take place every 6 months or as needed. The interim PFS analysis review may be combined with periodic safety review into one single review meeting if deemed sufficiently close. All analyses for IDMC review will be prepared by an external group not affiliated to the study team. The IDMC will provide a recommendation to the Sponsor per the IDMC charter after each review. For interim PFS futility analysis, the IDMC will recommend the Sponsor to continue or stop the study. However, the final decision will remain with the Sponsor.

Further details regarding the IDMC are provided in a separate IDMC Charter.

3.2 Interim Analysis

An interim non-binding futility analysis for the primary endpoint of PFS will occur approximately CCI from the date of the first participant being randomized into the study. It will be performed by an independent statistical group that has no direct contact with the study team. The interim analysis results will be reviewed by the IDMC, when at least CCI have occurred.

The same analysis method used for the primary efficacy endpoint (log-rank test as per Section 5.7.2) will be used for the interim analysis of PFS. To declare futility, CCI The actual boundary used will be recalculated based on the number of actual PFS events analyzed at the time of analysis.

The interim analysis will be conducted such that the ongoing study integrity is maintained. Only the independent statistical group, who is responsible for providing the interim analysis results to the IDMC, will be unblinded to the individual treatment group assignments. Interim analysis results will not be shared with investigators, participants, or the study team who are involved in the conduct of the study before the final database lock.

The interim analysis will include a summary of median PFS by treatment arm along with a 95% confidence interval (CI), calculated using the Kaplan-Meier (KM) product-limit method. Additionally, a figure of the KM estimator for PFS by treatment arm will be produced. Results of a stratified log-rank test and corresponding p-value will be provided, the stratification factor being the randomization strata (disease setting: at initial diagnosis or at first relapse after chemotherapy).

Finally, the HR and associated 95% CI for cabozantinib plus BSC relative to BSC alone will be produced, based on a Cox proportional hazards model stratified on the randomization strata.

3.3 Final Analysis

A cut-off date will be determined for the final analysis. CCI The alpha level for final analysis will be recalculated based on the actual number of interim PFS events and final PFS events analyzed at the time of each analysis.

4 ANALYSIS SETS

Screened Set

The screened set will contain all participants who signed an informed consent form.

Randomized Set

The randomized set will contain all participants who were randomized to study treatment. A participant will be considered as randomized if a treatment group has been assigned by the IWRS. For analyses and displays, participants will be classified according to randomized treatment.

Safety Set

The safety set will contain all participants who receive at least one dose of study treatment (study treatment referring to cabozantinib or BSC). For analyses on the safety set, participants will be classified according to treatment received. If there is any doubt whether a participant was treated or not, they will be assumed treated for the purposes of analysis. Safety data will be evaluated using the safety set.

Intent-To-Treat (ITT)

The ITT set will contain all participants from the randomized set (the term ITT set is used interchangeably with the randomized set). Efficacy will be evaluated based on the ITT analysis set. Generally, the term ITT set will be used for efficacy outputs.

If a participant has been randomized with an incorrectly determined randomization strata (disease setting), analyses that involve the stratification factor should use the uncorrected working strata per IWRS unless specified otherwise.

5 STATISTICAL METHODS/ANALYSES

The statistical analyses will be performed in accordance with the ICH E9 guideline and guidelines presented in Section 7.

5.1 General Considerations

All statistical analyses will be performed using the Statistical Analysis System® (SAS) software version 9.4 or a later version.

Where required to be shown by age group, analyses will be presented by the following:

- Pediatric population (<18 years, based on European Union Drug Regulating Authorities Clinical Trials Database [EudraCT] age category of children [5-11 years] and adolescents [12-17 years])
- Adult population (18 to 30 years)
- Overall

5.1.1 Definition of Study Periods

Study Periods are defined as shown in Table 5-1 below.

Table 5-1: Study Period Definitions

Period	Start Date	End Date
Open-label Treatment Period	Open-label Cycle 1 Week 1 Day 1	Date of open-label EOSI, or 1 day prior to start of switch treatment period for switch participants
Switch Treatment Period	Switch Cycle 1 Week 1 Day 1	Date of switch EOSI
Follow-up Period	One day after end of open-label treatment period, or one day after	Date last known date alive, or date of death

Period	Start Date	End Date
	switch after switch treatment period for switch participants	

5.1.1.1 Open-Label Treatment Period

The open-label treatment period serves as the primary analysis phase of the study. Unless otherwise specified, the analyses outlined in this plan pertain mainly to this phase.

5.1.1.2 Switch Treatment Period

While treatment remains open-label throughout the study, the switch treatment period represents a distinct clinical context due to differences in disease prognosis. Therefore, the main analyses will focus on the open-label treatment period. Analyses of data from the switch treatment period will be considered exploratory and conducted contingent upon the availability of sufficient data.

5.1.2 Output Presentation

5.1.2.1 Table Headers

Summary tables will be presented as follows:

- Disposition, demographic and baseline characteristics, major protocol deviations: by treatment group and overall
- Exposure and dose modification, and safety data (including AEs): by treatment group

5.1.2.2 Presentation of Treatment Groups

TFLs will display treatment groups using the following treatment group short labels shown in Table 5-2 below.

Table 5-2: Treatment Groups

Treatment Group	Treatment Group Short Label
Cabozantinib plus BSC	Cabozantinib + BSC
BSC alone	BSC
Switched to Cabozantinib plus BSC	Switched to Cabozantinib + BSC

5.1.2.3 Presentation of Visits / Timepoints

Summaries by visit will be presented using visit number as derived from the eCRF. Visits will be presented in the TFLs as CXWYDZ for those visits during the treatment period, where CX refers to the cycle number (C1 = Cycle 1, C2 = Cycle 2, etc.), WY refers to the study week (W1 = Week 1, W2 = Week 2, etc.) and DZ refers to the study day (D1 = Day 1, D2 = Day 2, etc.). The end of study intervention visit will be recorded in TFLs as EOSI.

5.1.3 Descriptive Statistics

All raw and derived variables will be listed and described using summary statistics. For categorical variables, summary statistics will be displayed using descriptive statistics by

frequency count and percentages by category. A separate "Missing" category will be presented if applicable. Participants with missing data will be included in the calculation of percentages unless otherwise specified. For quantitative variables, summary statistics will be displayed using descriptive statistics by number of observations, mean, standard deviation (StD), first quartile, median, third quartile, minimum and maximum, unless specified otherwise.

5.1.4 Baseline Value

Unless otherwise specified, open-label baseline is defined as the last assessment (including unscheduled and repeated assessments) performed prior to the first dose of IMP (including cabozantinib or BSC), or on or before C1W1D1 if the participant did not receive study treatment during open-label treatment period. Open-label baseline for efficacy endpoints is defined as the last non-missing measurement (including unscheduled and repeated assessments) on or prior to the date of randomization.

5.1.5 Reference Start Date and Study Day

Unless otherwise specified, reference start date is defined as the earliest start date of (cabozantinib or BSC medication [BSCM] or BSC radiotherapy [BSCR]).

The reference start date for efficacy endpoints is defined as the date of randomization.

The reference start date will be Day 1. Study day will be calculated based on that date as:

- The difference between the event date and the reference date plus one day, if the event is on or after the reference date.
- The difference between the event date and the reference date, if the date of event is prior to the reference date.

In case of partial or missing event date, study day will appear missing while any associated durations will be presented based on the partial/missing imputation rules described in Appendix A2.

5.2 Randomization, Disposition and Analysis Sets

A listing presenting randomization details will be provided.

The following disposition summaries and listings will be provided:

- Summary table with the number of participants screened, screen failed, and reason(s) for screening failure on the screened set.
- Disposition summary table on the randomized set with the number and percentages of:
  - Randomized participants
  - Participants randomized but not treated
  - Treated participants
  - Participants on open-label treatment
  - Participants who discontinued open-label treatment (including reason(s) for open-label treatment discontinuation)
  - Participants who switched to cabozantinib plus BSC (including participants who screen failed for switch, participants on cabozantinib switch treatment, and discontinued switch treatment (including reason(s) for discontinuation)

- Participants continuing to follow-up, including those who completed/did not complete follow-up and those remaining in follow-up
- Participants who discontinued or completed the study, including the reason(s) for study discontinuation/completion

Additionally, the disposition table will include descriptive statistics for the following:

- Overall duration of study (including follow-up) in months, which is defined as (last known alive date or death date - randomized date +1)/30.4375
- Overall potential duration of study (including follow-up) in months, which is defined as (data cutoff date – randomized date +1)/30.4375

- Listings for relevant disposition information will be generated.
- A flow chart of participant disposition, including relevant information from the disposition summary, on the screened set

5.3 Protocol Deviations

Major protocol deviations are a subset of protocol deviations which may significantly impact the completeness, accuracy, and/or reliability of key study data or that may significantly affect a participant's rights, safety, or wellbeing.

An exhaustive list of major protocol deviations that may occur during the course of the study and any action to be taken regarding exclusion of participants from analysis sets is defined in the Protocol Deviation Assessment Plan (PDAP). Major protocol deviations will be determined before final database lock, finalized during the planned analysis review and documented separately in the Planned Analysis Review Report (PARR).

The following outputs will be provided on the randomized set:

- A summary table of the number and percentage of participants with major protocol deviations by deviation category (see DV section of Standard Study Data Tabulation Model [SDTM] user guide)
- A listing of major protocol deviations, including protocol deviation category, description of protocol deviation and action for analysis

5.4 Demography and Other Baseline Characteristics

Demographic and baseline characteristics summaries and listings will be provided on the randomized/ITT set (the terms are used interchangeably). No statistical comparison between treatment groups will be performed.

Summaries will be provided on:

- Demographic variables and other baseline characteristics including: age, age group (5-<12 and 12-<18), sex, race, ethnicity, height, weight, body mass index (BMI), BMI group, BSA, Karnofsky performance status, and Lansky performance status

  Note: For the pediatric population, severe obesity is defined as a BMI greater than or equal to 1.2 times the value at the 95th percentile, or greater than or equal to 35 kg/m^2

  Note: Karnofsky performance status is collected for participants >=16 years of age only and Lansky performance status is collected for participants <16 years of age only.

- Baseline disease characteristics, including but not limited to:

- Time since histological or cytological primary diagnosis
- Osteosarcoma primary diagnosis area
- Primary tumor sites at diagnosis
- History of pathological fracture at diagnosis
- Morphological/Histological osteosarcoma tumor subtype
- Sum of diameters of target lesions at baseline
- Musculoskeletal tumor society (MSTS) (Enneking) staging at initial diagnosis and study entry
- American Joint Committee on Cancer (AJCC) staging for sarcoma in the appendicular skeleton, trunk, skull, and facial bones, and for spinal and pelvic tumors, at initial diagnosis and study entry
- Disease setting at enrollment per Interactive Response Technology (IRT) and per EDC
- Time since first relapse
- Number and percentage of participants who received prior chemotherapy for osteosarcoma, and time since prior chemotherapy
- Number and percentage participants who received prior radiotherapy, prior non-drug therapy, and who had a prior surgical procedure for osteosarcoma

Listings of demographics and baseline disease characteristics will be provided.

5.5 Medical History, Non-drug Therapies, Medications and Surgical Procedures

No summaries or listings will be provided for medical history, non-drug therapies, medications or surgical procedures.

5.6 Efficacy

No efficacy analyses will be performed. Only limited listings will be provided, including tumor assessments and QoL/acceptability and palatability.

5.6.1.1 Tumor Assessments

A listing of participants by treatment displaying RECIST v1.1 responses for target lesions, non-target lesions, new lesion response, and time point response (by BIRC and investigator assessment) by visit. For target lesions, sum of diameters, percentage change of sum from baseline nadir, and absolute percentage change of sum from post-baseline nadir will also be presented in the listing.

5.6.1.2 Patient-reported Outcomes

In participants less than 18 years of age, Patient-reported Outcomes (PRO) data will be provided by PedsQL Parent Report, PedsQL Report, PedsQL Cancer Module Parent Report, and PedsQL Cancer Module Report. Note that PRO assessments will be discontinued for BSC alone participants who switch to cabozantinib plus BSC.

The PedsQL Parent Report and Peds QL Report provide a score for the following subcategories, as well as a total score. The total score is the mean of all items; the physical health summary score is the same as the physical functioning score; and the psychosocial health summary score is the mean of the emotional, social, and school functioning subcategories scores:

- Physical functioning
- Emotional functioning
- Social functioning
- School functioning
- Psychosocial health
- Physical health

Similarly, the PedsQL Cancer Module Parent Report and PedsQL Cancer Module Report provide a score for the following subcategories as well as a total score:

- Pain and hurt
- Nausea
- Procedural anxiety
- Treatment anxiety
- Worry
- Cognitive problems
- Perceived physical appearance
- Communication

The rating for the individual PedsQL questions ranges from the following:

0- Never
1- Almost Never
2- Sometimes
3- Often
4- Almost Always

The following listing will be produced:

- A listing of PedsQL subcategory and total scores by questionnaire, participant, and visit

In adult participants, and participants aged 17 years or more at the time of enrolment, PRO data will be provided by the EORTC QLQ-C30 questionnaire.

The questionnaire provides a rating for a number of questions relating to QoL ranging from:

1- Not at all
2- A Little
3- Quite a Bit
4- Very Much

and scores for the following::

- Global Health Status/QoL
- Physical Functioning
- Role Functioning
- Emotional Functioning
- Cognitive Functioning
- Social Functioning
- Fatigue
- Nausea and Vomiting
- Pain
- Dyspnoea
- Sleep
- Appetite Loss
- Constipation
- Diarrhorea
- Financial Difficulties

The following listing will be produced:

- A listing of EORTC subcategory and total scores by participant and visit

5.6.1.3 Acceptability and Palatability

Acceptability and palatability of cabozantinib in children and adolescents will be assessed using a horizontal visual assessment scale (VAS) on Cycle 1 Week 1 Day 1.

The face scale to assess palatability has five response options – Very Bad, Bad, Neither Good or Bad, Good, Very Good – and the VAS score has a 0-100 scale (from 0=least palatable to 100 =most palatable)

The following listing will be provided:

- A listing of acceptability and palatability VAS data by participant.

5.7 Safety

5.7.1 General Considerations

Safety summaries and analyses will be based upon the safety set. All safety data will be included in participant data listings (see listing detail conventions in Appendix A4). There will be no

formal statistical comparison between the treatment groups for safety data. Instead, only descriptive analyses will be presented.

Baseline values are defined in Section 5.1.4. Unscheduled or repeat assessments will not be included in summaries by nominal visit, unless identified as a baseline, but will be included in the listings.

CTCAE version 5.0 will be used in the classification of AE severity. The relationship of AEs to IMP will be determined by the investigator.

5.7.2 Extent of Exposure

5.7.2.1 Duration of Study Treatment Exposure

Duration of study treatment exposure during open-label treatment period (including dose holds) will be calculated in months as the latest end date of (cabozantinib or BSCM or BSCR - earliest start date of (cabozantinib or BSCM or BSCR) +1*(12/365.25).

Summary statistics for duration of study treatment exposure, and the count and percentage of participants exposed for 3 months, 6 months, 12 months, 18 months, etc., will be presented. The duration of study treatment exposure will also be listed by participant.

5.7.2.2 Cabozantinib Treatment Exposure and Dose Modifications

Duration of cabozantinib exposure (including dose holds) will be calculated in months as (Date of last dose of cabozantinib – Date of first dose of cabozantinib + 1) * (12/365.25).

Duration of cabozantinib exposure (excluding dose holds) will be calculated in months as (Date of last dose of cabozantinib – Date of first dose of cabozantinib – Cumulative duration of dose holds + 1) * (12/365.25).

For the pediatric population, Total dose (mg/m^2) = Sum of all doses as (Actual cumulative dose [mg] / BSA closest to the start of dosing interval [m^2]).

For the adult population, Total dose (mg) = Sum of all actual cumulative doses (mg).

Average daily dose = Total dose / Duration of exposure (days) (including dose holds).

Dose intensity (%) = (Average daily dose / planned dose)*100, where planned dose for the pediatric population is 40 mg/m^2/day and for the adult population is 60 mg/day.

Dose modifications of cabozantinib will be defined as any dose reduction or interruption of cabozantinib, where a dose interruption (dose hold) is defined as any planned interruption to the administration of study treatment that is not a permanent stopping of treatment. Dose interruptions of cabozantinib will be summarized up until the last non-zero dose where participants receive IMP.

Dose reductions of cabozantinib will be allowed for the management of AEs associated with cabozantinib as follows: For the pediatric population (<18 years of age), cabozantinib dose reductions are shown in Table 5-3 below.

Table 5-3: Cabozantinib Dose Reductions for the Pediatric Population (<18 years of age)



For the adult population, dose reductions are shown in Table 5-4 below.

Table 5-4: Cabozantinib Dose Reductions for the Adult Population (≥18 years of age)

Assigned Dose	First Dose Level Reduction	Second Dose Level Reduction
60 mg of cabozantinib oral QD	40 mg of cabozantinib oral QD	20 mg of cabozantinib oral QD

Two dose reduction levels of cabozantinib are permitted. If a participant experiences a toxicity after two dose reductions, they must be removed from protocol therapy.

Children and adolescents with BSA range CCI and CCI will follow the same dosing strategy as adults.

The assigned dose for the adult population (≥18 years) is 60 mg QD. Two dose reductions will be permitted:

- 60 mg QD to 40 mg QD (first level dose reduction)
- 40 mg QD to 20 mg (second level dose reduction)

Study intervention must be discontinued if a QD dose of 20 mg cabozantinib is not tolerated.

The following outputs of cabozantinib dose modifications and extent of exposure will be presented:

- Summary of cabozantinib dose modifications, including the number and percentage of participants with dose modifications, dose interruptions, and dose reductions due to AEs, and time until first and second dose level reductions.
- Extent of cabozantinib exposure and dose modification information will be listed
- A batch listing for cabozantinib will also be provided

5.7.2.3 BSC Medication (BSCM) Treatment Exposure

The number and percentage of patients with BSCM by ATC code and preferred name will be presented.

A listing of BSCM treatment exposure will be provided.

5.7.2.4 BSC Radiotherapy (BSCR) Treatment Exposure

BSCR will be summarized for the number of radiation therapies received, intent of radiotherapy, and total dose in grays (Gy).

Detailed BSCR information will be listed.

5.7.3 Adverse Events

AEs and SAEs are defined in Sections 10.3.1 and 10.3.2 of the CSP, respectively.

All AEs recorded in the eCRF will be coded using MedDRA dictionary version 28.1 or later and graded by CTCAE version 5.0. TEAEs will be defined as follows:

Any AE with start date and time, or worsening severity, on or after the date and time of first dose of IMP (cabozantinib, BSCM, or BSCR) and up to the earliest of the following dates: date of death, date of lost to follow-up, date of consent withdrawal, date of last IMP + 30 days, or date of data cut-off.

Note: For open-label TEAE summaries, only TEAEs occurring prior to the date of Switch C1W1D1 will be included.

Appendix A2 describes the process for handling of partial/missing AE start or end dates. In cases where it is not possible to define whether an AE as treatment emergent or not, the AE will be classified by the most conservative case, i.e., treatment emergent. Only TEAEs will be included in summaries.

The following summary table will be provided for TEAEs in the open-label treatment period:

- An overview of TEAEs, showing the number and percentage of participants with at least one of the following: any AE (including both non-TEAEs and TEAEs), any TEAE, any treatment-related TEAE (TRAE), worst CTCAE grade 3 or 4 TRAE, fatal TEAE, an non-serious TEAE, any serious TEAE, any AESI, any ETM, any TEAE leading to dose reduction, interruption, or treatment discontinuation

Summaries of the number and percentage of participants reporting the following:

- TEAE by PT
- TEAE by SOC and PT
- TEAE by SOC, PT and CTCAE grade
- TRAEs by SOC and PT

- CTCAE Grade 3 or 4 TEAEs by SOC, PT and relationship to study drug (any treatment, cabozantinib, BSCM, and BSCR)
- Serious TEAEs by SOC, PT and relationship to study drug (any treatment, cabozantinib, BSCM, and BSCR)
- TEAEs leading to dose modifications (treatment modification is defined as any IMP dose reduced or drug interrupted)
- TEAEs leading to dose interruption
- TEAEs leading to dose reduction
- TEAEs leading to treatment discontinuation (drug withdrawn)

AEs will be counted as follows:

- Participants with more than one AE within a particular SOC are counted only once for that SOC. Similarly, participants with more than one AE within a particular PT are counted only once for that PT
- Participants reporting a TEAE more than once within a SOC/PT will be counted under the worst-case grade (grade order: 5>4>3>2>1>missing) in by-grade summaries
- If the grade is missing for a TEAE, it will be considered as missing in by-grade summaries
- Participants reporting a TEAE more than once within a SOC/PT will be counted under the worst-case relationship to study medication (order: related > not related > missing) in by-relationship summaries
- If there is a change in the intensity, an additional AE should have been collected in the eCRF

In addition, a listing of all AEs (including both non-TEAEs and TEAEs) will be provided by age subgroup and treatment group.

5.7.3.1 Deaths, SAEs and AESIs (ETMs)

During the development of cabozantinib, a set of events to monitor (ETMs) were identified based on known association with tyrosine kinase inhibitor (TKI) or vascular endothelial growth factor (VEGF) pathway inhibition. These events were selected due to their potentially serious outcomes or were determined to warrant ongoing safety surveillance. These comprise hepatobiliary disorders, decreased lymphocyte count, decreased neutrophil count, hair color changes, skin hypopigmentation, gastrointestinal perforation, abscess (all, intra-abdominal, and pelvic), fistula, wound complication, osteonecrosis, hemorrhage, hypertension, proteinuria, Palmar-plantar erythrodysaesthesia syndrome (PPES), Posterior reversible encephalopathy syndrome (PRES, also known as Reversible posterior leukoencephalopathy syndrome [RPLS]), arterial thromboembolic events, venous/mixed thromboembolic events, QT prolongation, renal failure, hepatotoxicity, embryotoxicity, and carcinogenicity. Additionally, growth plate thickening has been added on the list of AESI (ETMs) in this study for safety monitoring in pediatric participants.

Each ETM represents a grouped clinical term comprising a set of AEs that are related pathophysiologically. The groupings provide a consistent, reproducible, and transparent compilation of safety information over time. The method used to identify the AEs grouped within each ETM varies between ETM and can include one or more of the following: MedDRA tool (e.g., Standardized MedDRA Queries [SMQs]), high level group terms, and/or customized

lists of relevant PTs. As safety data accumulates, the identification and search criteria for ETMs may evolve. A final list of ETMs and their associated PTs will be provided in a listing.

Summaries will only include the final list of ETMs identified by the sponsor.

The following summaries and listings of deaths, SAEs, and ETMs will be provided:

- Summary of deaths by primary cause of death (AE, disease progression, or other)
- Summary of ETMs by ETM Group and PT, showing the number of ETMs, and number and percentage of participants with any ETM
- Summary of SAEs by primary SOC and PT
- A listing of deaths that occurred during the study
- A listing of AEs (including SAEs, AEs leading to discontinuation, and ETMs)

5.7.4 Laboratory Data

All laboratory data will be presented in the units of the International System of Units (SI). Clinically significant abnormalities will be reported as AEs.

The following listings are to be provided:

- Listings of all laboratory data (hematology, clinical chemistry, urinalysis (full testing, dipstick, and microscopic urinalysis), and coagulation

5.7.5 Vital Signs

The following listing is to be provided:

- A listing of vital sign data by treatment group, with abnormal values highlighted.

5.7.6 Electrocardiogram (ECG)

ECG results from the central laboratory will be used.

The following quantitative ECG measurements will be taken during the study:

- Heart rate (bpm)
- RR interval (msec)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- Fridericia corrected QT (QTcF) interval (msec)

An overall investigator assessment of ECG will be provided as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”.

Normal range for the QTcF is considered to be <=450 msec. A change in QTcF >60 msec above baseline is considered prolonged QT.

A listing of ECG data will be provided with PCSA and abnormal results flagged. This listing will include individual measurements as well as triplicate means.

5.7.7 Physical Examination

No summary tables will be produced of physical examinations, as any significant abnormality will be reported as an AE. However, the data will be listed by participant.

5.7.8 Tibial Radiographs (Growth Plate)

Tibial X-rays for all participants ≤18 years of age will be conducted. Participants with open growth plates at baseline will have further X-rays every 6 months until 1 year after last dose of IMP. Abnormal findings are reported as an AE.

The following listing will be provided:

- A listing of X-ray growth plate data

5.7.9 Measurement of Growth

Linear growth in participants <18 years of age will be assessed by changes in height. A listing of height, weight, and BMI data, including SDS and percentile results will be produced.

Assuming growth measurement follows the normal distribution, the SDS will be derived as the corresponding SDS at the given percentile.

5.8 Data Analysis Related to Switch Treatment Period

Switch participants are those that answered 'Yes' to 'Will subject switch over to Cabozantinib?' question on the open-label 'End of Study Intervention' form of the Electronic Case Report Form (eCRF) and have a date present for 'Switch Over Consent date' in the 'Switch- Informed Consent and Re-Consent' form of the eCRF. Switch participants who do not go on to receive cabozantinib and end the study after switching are considered switch screen failures.

For participants switching from BSC alone to cabozantinib plus BSC, the reference start date for post-switch visits is the date of Switch C1W1D1.

Data collected during switch treatment period will be included in the relevant listings.

5.9 Changes in the Conduct of the Study or Planned Analysis

Planned analyses per CSP will not be performed due to the decision to terminate the study early. Limited summaries will be provided for the abbreviated CSR due to the early termination decision.

6 DATA HANDLING

6.1 Visit Window

There will be no time windowing for visits/timepoints.

6.2 Unscheduled Visits, Retest, and Withdrawal Visit

All listings will include retests and unscheduled visits, while for the description by visit in the tables, only the scheduled visits as per the CSP will be described.

Unscheduled visit and retest measurements will be used to provide a measurement for baseline data or endpoint value (e.g., worst value), if appropriate, according to their definition. These measurements will also be used to determine abnormal laboratory, vital signs, or ECG values.

7 REFERENCES

Reference to ICH regulatory guidelines:

- ICH E3: Structure and Content of Clinical Study Reports
- ICH E6 (R2): Good Clinical Practice
- ICH E9: Statistical Principles for Clinical Trials
- ICH E9 (R1) Addendum: Estimands and Sensitivity Analysis in Clinical Trials

Reference to EMA or point to consider guidelines:

- Adjustment for baseline covariates in clinical trials
- Choice of a non-inferiority margin
- Clinical trials in small populations
- Data monitoring committees
- Investigation of subgroups in confirmatory clinical trials
- Missing data in confirmatory clinical trials
- Application with Meta Analyses, One pivotal study
- Multiplicity issues in clinical trials
- Switching between superiority and non-inferiority

Reference to FDA guidelines:

- Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics
- Multiple Endpoints in Clinical Trials

Standard Ipsen Study Data Tabulation Model (SDTM) user guide

Standard Ipsen Analysis Data Model (ADaM) user guide version 1.3

Ipsen Global Style guide

References for statistical methods:

- Greenwood, M. (1926) The natural duration of cancer. Reports on Public Health and Medical Subjects 33, 1-26. Her Majesty's Stationery Office, London.

References for RECIST v1.1 criteria:

- E.A. Eisenhauer et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer. 2009; 45:228-247.

8 APPENDICES

A1. List of PCSA Criteria

PCSA for ECG parameters are shown in Table 8-1 below.

Table 8-1: PCSA for ECG Parameters

Parameter	Population	PCSA
QTcF	All participants	<=450 msec >450 msec - <=480 msec >480 msec - <=500 msec >500 msec
Delta QTcF	All participants	>60 msec increase from baseline

A2. Partial/Missing Date Convention

In all listings, missing or incomplete dates should be left as they have been recorded.

Algorithm for TEAE

For deriving the TEAE flag the following process of temporary date imputation is done (for AE start date only assuming no AE end date are missing). The date imputation algorithm for incomplete adverse event start dates is described in Table 8-2. Classification of adverse event according to its treatment-emergent status is then done using the imputed date. The date imputation algorithm for incomplete adverse event end dates is described in Table 8-3, assuming the latest possible date.

Table 8-2: Data Imputation Algorithm for AE Start Dates (ADSTDT) with Reference Start Dates (as per Section 5.1.5) on 2002-08-11

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-07-XX	2002-07-01
YYYY-MM = YYYY-MM of [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-08-XX	Min (2002-08-11, AE end date)
YYYY-MM > YYYY-MM of [First IMP admin.]	YYYY-MM-01	2002-09-XX	2002-09-01
Day and month are missing			
YYYY < YYYY OF [First IMP admin.]	YYYY-01-01	2001-XX-XX	2001-01-01
YYYY = YYYY OF [First IMP admin.]	Min ([First IMP admin.], AE end date)	2002-XX-XX	Min (2002-08-11, AE end date)
YYYY > YYYY OF [First IMP admin.]	YYYY-01-01	2003-XX-XX	2003-01-01
Day, month, and year are missing			
XXXX-XX-XX	Min ([First IMP admin.], AE end date)		Min (2002-08-11, AE end date)

Dates are presented using YYYY-MM-DD format.
YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field.

If an AE onset date is partial or missing, the event will be allocated to the first IMP administration where onset could have occurred (taking date and time stopped into account).

Table 8-3: Data Imputation Algorithm for AE End Dates (AENDT) with Last Visit/Contact Date on 2022-02-22 (for AE not ongoing as EOS)

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day is missing			
YYYY-MM < YYYY-MM of [Last visit/contact]	YYYY-MM-31	2021-07-XX	2021-07-31
YYYY-MM = YYYY-MM of [Last visit/contact]	YYYY-MM-22	2022-02-XX	2022-02-22

Description of incomplete date	Imputed numeric date	Example	
		Character date	Imputed date
Day and month are missing			
YYYY < YYYY of [Last visit/contact]	YYYY-12-31	2021-XX-XX	2021-12-31
YYYY = YYYY of [Last visit/contact]	YYYY-02-22	2022-XX-XX	2022-02-22
Day, month, and year are missing (AE not ongoing at Eos)			
XXXX-XX-XX	No imputation	XXXX-XX-XX	

Dates are presented using an YYYY-MM-DD format.
YYYY = non-missing year, MM = non-missing month, DD = non-missing day, XX = missing field

AE duration will be calculated using the start and end date of the AE as end date – start date + 1. In case of partial start/end dates, the temporary imputed date will be used and the duration will be reported as "≤ xx" since at least one date is imputed and maximized.

In case of ongoing AEs (e.g., at the end of the study or at the time of interim analysis):

- If the start date is complete, the duration will be reported as "≥ xx" and the date of end of study date or last attended visit will be considered as end date
- If start date is incomplete, the duration is not calculated

A3. Programming Convention for Outputs

All text fields must be left justified and numeric or numeric with some text specification (e.g.: not done, unknown, <4.5, …) must be decimal justified.

The mean, median, lower quartile, upper quartile, StD and standard errors (SE) of the mean 95% CI values will be reported to one decimal place greater than the raw data recorded in the database.

The minimum and maximum values will be reported with the same number of decimal places as the raw data recorded in the database.

In general, the maximum number of decimal places reported should be four for any summary statistic.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentage will be calculated using n as denominator. The denominator n will be specified in a footnote for clarification if necessary. If sample sizes are small (n<15), the data displays will show the percentages, but in the CSR only frequency counts should be described.

P-values will be reported to four decimal places (e.g.: p=0.0037), after rounding. P-values which are less than 0.0001 will be presented as '<0.0001'.

All values below or above a limit of detection (e.g. <0.1 or >100) will be listed as such. However, for the purpose of analyses, values below or above a limit of detection will be imputed as the limit of detection (e.g. 0.1 or 100).

Dates will be presented in the format [ddmmmyyyy] and times in the format [hh:mm].

A4. Listings Conventions

Any listings will contain at least the following data: participant identifier, age and gender. When dates are presented, the associated study days should be included. They should be sorted by treatment group then participant identifier.