A Phase 1, Open-label Study to Assess Copper Balance in Healthy Participants Following Administration of ALXN1840

Unique Protocol ID:	ALXN1840-HV-108
NCT Number:	NCT04594252
EudraCT Number:	2019-003010-14
Date of SAP:	20 July 2020

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: ALXN1840-HV-108

A PHASE 1, OPEN-LABEL STUDY TO ASSESS COPPER BALANCE IN HEALTHY PARTICIPANTS FOLLOWING ADMINISTRATION OF ALXN1840

Author: PPD

Date: 20 July 2020

Version: 1.0 Final

1. APPROVAL SIGNATURES

PPD

20-Jul-2020 | 16:51:01 EDT

Date dd Mmm yyyy

20-Jul-2020 | 16:53:05 EDT

Date dd Mmm yyyy

20-Jul-2020 | 18:53:18 EDT

Date dd Mmm yyyy

20-Jul-2020 | 20:49:52 EDT

Date dd Mmm yyyy

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this statistical analysis plan (SAP).

Table 1: Abbreviations and Acronyms

Abbreviation or acronym	Explanation
λ_z	apparent terminal-phase elimination rate constant
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AR	accumulation ratio
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the plasma concentration versus time curve
AUC_t	AUC from time 0 to the last quantifiable concentration
AUC_{tau}	AUC over the dosing interval
AUC_∞	AUC from time 0 to infinity
AUEC	area under the effect versus time curve
$AUEC_t$	AUEC from the start of dose administration to the last observed quantifiable concentration
BLQ	below the limit of quantification
BMI	body mass index
CL/F	apparent total body clearance
CE_{max}	maximum observed effect after dosing
C_{max}	maximum observed concentration
Cp	ceruloplasmin
CpC	ceruloplasmin-bound copper
CRF	case report form
CRU	clinical research unit
C_τ	observed concentration at the end of the dosing interval
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough (predose) concentration observed at the start of the dosing interval
Cu	copper
CV	coefficient of variation
ECG	electrocardiogram
EOS	End of Study
FA	Full Analysis
GM	geometric mean
ICH	International Conference on Harmonization
ICF	informed consent form
ICP-MS	inductively coupled plasma mass spectrometry
INR	International Normalized Ratio
I/O	input/output
LBC	labile bound copper
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
Mo	molybdenum
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	non-ceruloplasmin-bound Cu concentration corrected for the amount of Cu bound to the Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration

Table 1: Abbreviations and acronyms (Continued)

Abbreviation or acronym	Explanation
NCI	National Cancer Institute
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
PTAE	pre-treatment adverse event
PUF	plasma ultrafiltrate
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SAS®	Statistical Analysis Software®
SD	standard deviation
SoA	Schedule of Activities
SOC	System Organ Class
SRC	Safety Review Committee
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TE_{last}	time after dosing at which the last quantifiable concentration was observed
TE_{max}	time after dosing at which the maximum effect was observed
T_{lag}	time delay between the time of dosing and time of appearance of Mo concentration in plasma
T_{last}	time of last quantifiable concentration
T_{max}	time to maximum concentration
V_d/F	apparent volume of distribution
WHO	World Health Organization

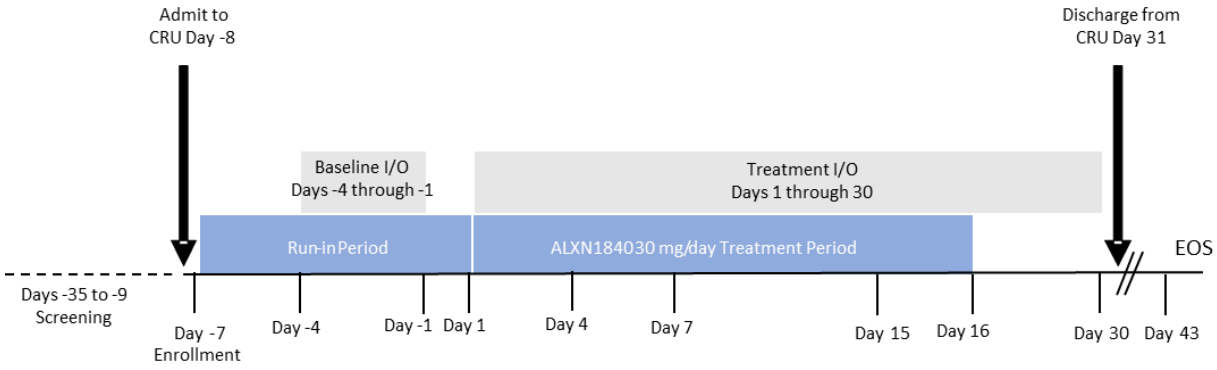
4. DESCRIPTION OF THE PROTOCOL

Study ALXN1840-HV-108 is a single-arm, open-label, repeat-dose (30 mg/day) study designed to assess the effects of ALXN1840 administration on copper (Cu) balance in healthy participants.

Approximately 17 participants will be enrolled and will receive study drug to achieve 13 evaluable participants who complete the study (Appendix 9.1). This study will be conducted in a minimum of 2 groups. The first group will consist of approximately 6 participants and no more than 8 participants. The second group may only be initiated after the Safety Review Committee (SRC; defined in Section 9.7 of the Protocol) reviews safety information (all adverse events [AEs], safety laboratory data, and vital signs) through Day 18 and agrees that it is safe to continue enrollment to complete the study. If ceruloplasmin (Cp) concentrations or AE findings are suggestive of over-depletion of Cu, the SRC may propose a dose reduction to 15 mg/day for the remainder of the study population.

This is a single arm study. Following Screening and enrollment, participants will have a Run-in Period to support diet equilibration (Day -7 through Day -5) and measurement of pretreatment Cu and molybdenum (Mo) balance (Day -4 through Day -1). Following the Run-in Period, participants will be administered ALXN1840 at 30 mg/day for 15 days (Day 1 through Day 15). ALXN1840 will be administered orally after an overnight fast, and participants will remain fasted for a minimum of 2 hours following each dose administration. Following completion of the 15-day dosing period, participants will remain the clinical research unit (CRU) for an additional 16 days until discharge on Day 31. The study design schematic is presented in Figure 1.

Figure 1: Study Design Schematic



Participants will be admitted to the CRU on Day -8 and discharged on Day 31.
Participants eligible for the study will be enrolled (assigned a subject number) on Day -7. A Cu- and Mo-controlled diet will be initiated on Day -7 and will be continued through Day 30.
Participants will be administered ALXN1840 at a dose of 30 mg/day from Day 1 through Day 15, with the Post-treatment Period starting at Day 16.
Total intake and total output (I/O) samples for measurement of Cu and Mo will be collected during the Baseline (Day -4 through Day -1), Treatment (Day 1 through Day 15), and Post-treatment Periods (Day 16 through Day 31). I/O defines the period in which all intake (food and drink) and all output (urine and feces) will be collected for the measurement of Cu and Mo.

Total intake and output of Cu and Mo will be measured continuously from Day -4 through Day 30 with Day 1 through Day 15 representing the ALXN1840 Treatment Period and Day 16 through Day 30 representing the Post-treatment Period. The collection period will support

assessment of Cu balance and Mo mass balance including assessment at steady state and terminal elimination.

Participants will return to the CRU for a final study visit on Day 43 ± 2 days, approximately 28 days after the final dose of ALXN1840, to conclude the Safety Follow-up Period.

Participants meeting all study entry criteria prior to Cu/Mo controlled diet initiation are eligible for enrollment. At the time of enrollment, participants will be assigned a subject number for the study.

Throughout the period in the CRU, participants will remain on a Cu- and Mo-controlled diet with a limited selection of meals utilized for breakfast, lunch and dinner throughout the study to ensure Cu/Mo control (refer to Protocol Table 4). During the intake and output collection periods, daily urine will be pooled (24-hour collection) with volumes recorded for each 24-hour period. Fecal samples will be individually collected; each sample will include a collection date, time, and weight. To support accurate determination of daily Cu/Mo content for each 24-hour period, participants should be encouraged to provide urine and fecal sample (if appropriate) prior to 0800 or the dosing time each morning. To support assessment of daily Cu/Mo balance, on Days -4 through Day 30, at every mealtime, an additional meal will be prepared from the same batch as the meals being given to the study participants and will be analyzed for Cu and Mo content. A minimum of 3 complete meals from each prepared batch will be sent for analysis.

Copper balance is defined as the difference between the measured Cu input via food and drink, and the measured Cu elimination in urine and feces, and will be calculated as the average daily Cu balance over the collection period. For assessment of ALXN1840 effect on Cu balance, the time period for analysis will take into consideration the average bowel transit of approximately 40 hours (male: 33 hours; female: 47 hours) (Camilleri, 1986; Metcalf, 1987; Weaver, 1984). Collection over the entire 15 days of ALXN1840 treatment allows a robust average assessment of Cu balance and ensures a complete assessment of Mo absorption, distribution, metabolism, and excretion (ADME). The study assumes insensible loss due to sweat does not change significantly with ALXN1840 treatment and is, therefore, not measured. While menstruation is not anticipated to significantly impact Cu/Mo balance, it may have a minor impact on interpretation of the urine data. Dates of menstruation should be collected to help support data interpretation.

Molybdenum mass balance, as a measure of ALXN1840 ADME, will be calculated in an analogous fashion to Cu balance; however, the Mo balance will also include the Mo content in ALXN1840 as part of the Mo intake in the calculation. Following the final ALXN1840 dose administration on Day 15, intake and output collection will continue through Day 30 to characterize the extent of Mo and Cu elimination, which may allow for better understanding of Mo and Cu elimination after dose discontinuation.

Intensive blood sampling for pharmacokinetic (PK)/pharmacodynamic (PD) analyses will occur over the 24-hour dosing periods on Day 1 and Day 15. Additional PK/PD sampling will occur as noted in the Schedule of Activities (SoA) in the Protocol Table 1.

4.1. Changes From Analyses Specified in the Protocol

Not applicable. There are no changes from the protocol.

4.2. Changes From Analyses Specified in the Previous Version of the Statistical Analysis Plan

Not applicable. This is the first version of the SAP.

5. DEFINITIONS

5.1. Efficacy

There are no efficacy assessments performed during this study.

5.2. Copper and Molybdenum Balance Measurements

Copper and Mo balance measurements will be made on all intake (ie, study drug, food, and fluids) and all output (urine and feces) from participants as indicated in the SoA. The Cu and Mo concentration of each sample will be determined by inductively coupled plasma mass spectrometry (ICP-MS). Copper and Mo content of all intake and output will be calculated based on the volume or weight of intake and output and the concentration of representative samples.

5.2.1. Primary Objective and Endpoint

The primary objective of this study is to assess change from Baseline in Cu balance over 2 weeks of repeated daily ALXN1840 dosing. The primary endpoint is the change in mean daily Cu balance from pretreatment Baseline Period to ALXN1840 Treatment Period, as measured by the calculated difference between Cu intake (in food and drink), and Cu output (in feces and urine).

5.2.1.1. Food and Fluid Collection for Copper and Molybdenum Concentrations

Samples of all meal and fluid batches will be collected and analyzed for measurement of Cu and Mo content. A minimum of 3 complete portions/meals from each food and liquid batch will be sent for analysis. All participants will drink water from the same large water bottle dispenser. Samples of water from this dispenser will be collected and analyzed for Cu and Mo content.

Samples will be collected, stored and shipped as detailed in the Laboratory Manual. Copper and Mo concentration of each food sample (ng/g) and each fluid sample (ng/mL) sample will be determined by ICP-MS.

5.2.1.2. Urine Collection for Measurement of Copper and Molybdenum Content

Urine samples to measure Cu and Mo content will be taken from Day -4 through Day 30, as described in the SoA (Protocol Table 1). Samples will be collected, stored and shipped as detailed in the Laboratory Manual. For each 24-hour collection period, urine will be pooled for analysis and volumes will be recorded.

Copper and Mo concentration (ng/mL) of each 24-hour urine sample will be determined by ICP-MS.

5.2.1.3. Fecal Collection for Measurement of Copper and Molybdenum Content

Fecal samples to measure Cu and Mo content will be taken from Day -4 through Day 30 as described in the SoA (Protocol Table 1). Samples will be collected, stored and shipped as detailed in the Laboratory Manual. Fecal samples will be individually collected, weighed and stored. The weight and time of each bowel movement will be recorded.

Copper and Mo concentration (ng/g) of each stool sample will be determined by ICP-MS; each sample will be analyzed using a minimum of technical triplicates.

5.2.2. Secondary Objectives and Endpoints

The secondary objectives and endpoints are:

Objectives	Endpoints
Assess net copper (Cu) balance over 2 weeks of repeated daily ALXN1840 dosing	Mean daily Cu balance during ALXN1840 Treatment Period where Cu balance is measured by the calculated difference between Cu intake (in food and drink), and Cu output (in feces and urine)
Assess steady-state molybdenum (Mo) balance after 2 weeks of repeated daily ALXN1840 dosing	Mean daily Mo balance at ALXN1840 pharmacokinetic (PK) steady state, as demonstrated through measurement of Mo intake (in food, drink, and ALXN1840), and Mo output (in feces and urine)
Assess extent of Mo excretion in urine and feces	Quantify total Mo excretion in urine and feces following ALXN1840 treatment compared with Baseline
Determine the steady-state plasma PK of ALXN1840 after 2 weeks of repeated daily ALXN1840 dosing	PK parameters for plasma total Mo and plasma ultrafiltrate (PUF) Mo including terminal elimination for Mo after steady-state dosing
Investigate the effect of ALXN1840 on the disposition of Cu after 2 weeks of repeated daily ALXN1840 dosing at steady state	Cu quantified in food, feces, and urine over 2 weeks of ALXN1840 dosing including plasma total and labile bound Cu (LBC) at steady state
Investigate the effect of ALXN1840 on the disposition of Cu over 2 weeks of repeated daily ALXN1840 dosing and through the Post-treatment Period	Cu quantified in food, drink, feces, and urine
Investigate the effect of ALXN1840 on the disposition of Mo over 2 weeks of repeated daily ALXN1840 dosing and through the Post-treatment Period	Mo quantified in ALXN1840 doses given and in food, drink, feces, and urine

5.2.3. Exploratory Objectives and Endpoints

The exploratory objectives and endpoints are:

Objectives	Endpoints
Assess the effects of ALXN1840 on ceruloplasmin (Cp), ceruloplasmin-bound Cu (CpC), and labile bound copper (LBC) profiles in plasma	Absolute and percent changes in Cp, CpC, CpC:Cp ratio, and LBC during Treatment Period and post-treatment compared with predose Baseline
Assess the effects of repeated daily ALXN1840 dosing on Cu:Mo ratio in plasma at steady state	Measure plasma Cu:Mo ratios during Treatment Period and post-treatment compared with predose Baseline
Assess the effects of ALXN1840 on Cu:Mo ratio in urine and feces	Measure the average daily Cu:Mo ratio in urine and feces during treatment and post-treatment compared with predose
Assess the effects of ALXN1840 on the time course of Cu balance over 2 weeks	Evaluate the effect of time on change in average daily Cu balance

5.3. Safety

The safety objective of this study is to evaluate the safety and tolerability of repeated dose administration of ALXN1840 in healthy participants. Treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs), clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis), and physical examinations will be evaluated. Heart rate, intervals (PR, QRS, interval between the start of the Q wave and the end of the T wave in an electrocardiogram (ECG) (QT), and QT interval corrected [QTc]), clinically significant ECG findings as determined by triplicate 12-lead ECG will be assessed, and vital sign assessments

(body temperature, blood pressure, respiratory rate and heart rate) will be measured. The SoA is provided in Table 1 of the Protocol.

5.3.1. Adverse Events

All AEs will be reported to the Investigator or qualified designee by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until the End of Study (EOS) Visit.

Each AE will be characterized (ie, verbatim term) and information regarding its seriousness, start and stop dates, toxicity, outcome, and causal relationship with the study drug will be provided. The safety evaluation will include an assessment of all AEs, SAEs, AE toxicity, and AE relatedness to study drug. Adverse event toxicity will be evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (published 27 Nov 2017) (NCI, 2017). Further details are given in the Protocol Section 8.3 and Protocol Appendix 3.

5.3.2. Laboratory Assessments

Clinical laboratory measures include chemistry, hematology, coagulation, urinalysis and other tests.

Participants' bowel movements and urination will be monitored by the clinical staff. The clinical staff will record each time a fecal and urine sample is collected in the case report form (CRF).

To support accurate quantification of Cu/Mo intake, each participant's intake including both food and fluids will be monitored and recorded. Following each standardized meal, the clinical staff will record 100% completion of each meal including all liquids. If a participant is unable to eat 100% of the food for a given meal, the remaining food will be weighed and reported in the CRF to support accurate determination of Cu/Mo as a fraction of the total meal. Similarly, if participants do not complete 100% of non-water fluids with meal, the remaining volume will be measured and recorded in the CRF. In the case of water intake, the staff will record daily water volume intake in the CRF.

Clinically significant laboratory values are those deemed by the Investigator to be clinically significant resulting in further evaluation or treatment or those associated with an AE or clinical signs or symptoms. All laboratory test results with values considered abnormal and clinically significant during participation in the study after the last dose of study drug should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or medical monitor.

The specific laboratory assessments are provided in Section 10.2 of the Protocol.

5.3.3. Vital Signs

Vital signs will be measured in a semi-supine position after a five-minute rest and will include body temperature, heart rate (beats/min), respiratory rate, and systolic and diastolic blood pressure (mmHg). Readings will consist of a single pulse and blood pressure measurement. If vital signs are abnormal as defined by inclusion/ exclusion criteria, 2 additional vital signs

measurements will be made. The mean of the 3 vital signs measurements will be recorded in the CRF and used to determine participant eligibility.

5.3.4. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height (at Screening only) and weight (as per the SoA for physical examinations) will also be measured and recorded. A symptom-driven physical examination may be performed at other times, at the Principal Investigator's discretion.

5.3.5. Electrocardiograms

Triplicate 12-lead ECGs will be conducted as outlined in the SoA (Protocol Table 1) to obtain heart rate, PR interval, RR interval, QRS duration, QT interval, and QTc interval. If ECG interval measurements are abnormal, an additional 2 replicate measures will be performed with the mean of the 3 measured interval values used to confirm eligibility and recorded in the CRF.

5.4. Pharmacokinetics and Pharmacodynamics

5.4.1. Pharmacokinetics

Whole blood samples will be collected for the measurement of plasma concentrations of total and plasma ultrafiltrate (PUF) Mo as specified in the SoA via ICP-MS. Samples will be used to evaluate the PK of ALXN1840. Samples collected for analyses of plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study. The actual date and time (24-hour clock time) of each sample will be recorded.

5.4.2. Pharmacodynamics

Plasma total Cu, Cp, CpC, PUF Cu, non-ceruloplasmin-bound Cu (NCC), and labile bound Cu (LBC) will be assessed during the study.

Blood samples will be collected as described in the SoA (Protocol Table 1) for plasma isolation as per the Laboratory Manual. The isolated plasma will be stored at -20°C before analysis. Plasma samples will be used for ICP-MS measurement of total Cu, Cp, CpC, PUF Cu, and toxic Cu as measured by LBC and/or NCC at the time points indicated in the SoA.

6. DATA SETS ANALYZED (STUDY POPULATIONS)

6.1. Screened Set

All participants who signed the ICF.

6.2. Enrolled Set

All participants who signed the ICF, were eligible for the study, and were registered on Day -7.

6.3. Full Analysis Set

All participants who received at least 1 dose of ALXN1840. The primary analysis will be performed using the Full Analysis (FA) Set.

6.4. Per Protocol Set

All participants who received at least 1 dose of ALXN1840, had Baseline and all post-Baseline values of Cu intake (in food and drink) and Cu output (in feces and urine), and were 100% compliant with study drug dosing. Participants with major protocol deviations that are likely to impact the primary endpoint analysis will be excluded from the Per Protocol (PP) Set. Major protocol deviations, and the PP Set, will be defined, documented, and agreed within Alexion prior to database lock.

6.5. Safety Set

All participants who received at least 1 dose of ALXN1840.

6.6. Pharmacokinetic/Pharmacodynamic Analysis Set

All participants who have sufficient samples to enable the calculation of PK parameters and provide PK/PD profiles.

7. STATISTICAL ANALYSIS

Summary statistics will be computed and displayed by day and period (pre-dose Baseline, treatment, steady state, and post-treatment), where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Analyses will be performed using the SAS® (Statistical Analysis Software®) software Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina).

In general, analyses will be presented by group (referring to the study being conducted in groups; see Section 4) and overall, where specified.

7.1. Study Participants

7.1.1. Disposition of Participants

The number and percentage of all participants screened, enrolled, and included in the Full Analysis (FA), PP, Safety, and PK/PD analysis sets will be summarized. The reasons for exclusion from the analysis sets will also be provided. Frequency counts and percentages of participants excluded prior to enrollment will be provided for participants who failed to meet study entry requirements during Screening.

The number and percentage of participants who completed, or prematurely discontinued from the study will be summarized by group and overall. For participants who discontinued the study, the number and percentage will be summarized by their reason for premature discontinuation. Additionally, the number of participants who completed or prematurely discontinued treatment and the reason for treatment discontinuation will be summarized. A summary of participants who did not meet inclusion or who met exclusion criteria will be provided.

Descriptive statistics of the number of days in the study will be summarized. The date of first and last use of the study drug, and the study termination date will be listed. Individual reasons for premature discontinuation from the study will be presented in a listing, as will the reason for premature discontinuation from study drug. All enrolled participants will be listed indicating their membership to each analysis set along with the reason for exclusion. Additionally, a listing of the inclusion/exclusion criteria and a listing of participants and the inclusion criteria they failed to meet and the exclusion criteria they met will be provided. A listing of screen failure participants will also be provided.

7.1.2. Protocol Deviations

All important/not important protocol violations will be determined and appropriately categorized prior to database lock. The number and percentage of participants with any important/not important protocol violations as well as the number and percentage of participants with violations within each category will be presented. A listing will also be provided.

7.1.3. Demographics, Baseline Characteristics, and History

All demographic and Baseline characteristics information will be summarized for the FA Set. Summary statistics will be presented by group and overall. Continuous variables will be

presented using descriptive statistics, and categorical variables will be presented using frequencies and percentages. Age will be calculated relative to informed consent and will be summarized as a continuous variable. Listings will also be provided.

7.1.3.1. Demographics

The following demographic variables will be summarized:

- Sex
- Race (where collection is permitted by local regulations)
- Ethnicity (where collection is permitted by local regulations)
- Age (years)
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)

7.1.3.2. Baseline Characteristics

The following Baseline characteristics will be summarized:

- LBC (µmol/L)
- LBC categorization based on normal reference range (female: <0.7 µmol/L, 0.7 to 5.9 µmol/L, >5.9 µmol/L; male: <0.9 µmol/L, 0.9 to 4.4 µmol/L, >4.4 µmol/L)
- NCC (µmol/L)
- NCC categorization based on normal reference range (<0.8 µmol/L, 0.8 to 2.3 µmol/L, >2.3 µmol/L)
- Albumin (g/L)
- International Normalized Ratio (INR)
- Total bilirubin (µmol/L)
- Direct bilirubin (µmol/L)
- Alanine aminotransferase (ALT) (IU/L)
- Aspartate aminotransferase (AST) (IU/L)
- Gamma-glutamyltransferase (GGT) (IU/L)
- Platelets (10^9/L)
- Leukocytes (10^9/L)
- Creatine Kinase (IU/L)
- Total Plasma Cu (µmol/L)

- Total plasma Cu; categorization based on normal reference range (low: < 11.33 µmol/L [< 720 ng/mL]; normal: 11.33 - 26.12 µmol/L [720 - 1660 ng/mL]; high: > 26.12 µmol/L [> 1660 ng/mL])
- PUF-Cu (µmol/L)
- Total plasma Mo (µmol/L)
- PUF-Mo (µmol/L)
- Cp (mg/L)
- 24-Hour urinary Cu (µg/day)
- 24-Hour urinary Mo (µg/day)
- Categorization of baseline lab values (ALT, AST, GGT, platelets, leukocytes, creatine kinase) based on the reference ranges (L: Low, N: Normal, H: High)

7.1.3.3. Medical/Surgical History and Physical Examination

Medical and surgical history will be summarized by counts and percentages and displayed by System Organ Class (SOC) and Preferred Term (PT) within each SOC. Both SOCs and PTs will be coded using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0 or higher, available at the start of the study. This dictionary will be used throughout the life of the study and will not be updated during the study conduct. The number and percentage of participants will be presented for ongoing conditions and previous conditions separately by SOC and PT. A listing will also be created.

For the physical examination, the number and percentage of participants with abnormal findings at each visit for each body system will be summarized and included in the data listing.

7.1.4. Prior and Concomitant Medications/Therapies

Prior medications will be defined as medications that were discontinued prior to the start of study drug. Concomitant medications will be defined as medications that either started prior to first dose of study drug and were continuing at the time of first dose of study drug or started on or after the date of the first dose of study drug. If it cannot be determined whether a medication was stopped prior to the start of study drug dosing due to partial or missing medication start or end dates, it will be considered a concomitant medication.

The World Health Organization (WHO) Drug Dictionary version from March 2018 or later will be used to code the medications. Medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class and generic drug name.

Prior and concomitant medications will be summarized separately for the FA Set by group and overall. The number and percentage of participants receiving any concomitant medication will be summarized, as well as the number and percentage receiving any concomitant medication by ATC drug class and generic drug name. Participants reporting use of more than 1 medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. All ATC class terms will be displayed alphabetically and generic drug names within each ATC class will be displayed by descending order of incidence.

Prior and concomitant medications will be presented in a data listing by participant and medication name.

7.2. Efficacy Analyses

No efficacy endpoints are included as part of this study; therefore, there is no analysis of efficacy.

7.3. Copper and Molybdenum Balance Analyses

The primary objective of this study is to assess the change from Baseline in Cu balance over 2 weeks of repeated daily ALXN1840 dosing (ALXN1840 treatment at 30 mg/day in healthy participants). Secondarily, the study will also assess whether a net negative Cu balance is achieved following ALXN1840 treatment. The study will also assess Mo balance at ALXN1840 PK steady state.

Copper balance is defined by the difference in Cu input and Cu output. A negative Cu balance will indicate greater Cu output than Cu intake. Copper input is defined as the sum of all Cu input as measured in all food and fluids over the specified period. Copper output will be defined as the sum of all Cu output as measured in urine and feces over the specified collection period. Many of the Cu inputs and outputs will be collected with technical replicates and the mean of the replicates will be utilized in the analysis. Daily balance values may also be calculated. The study assumes insensible Cu/Mo loss due to sweat does not change significantly with ALXN1840 treatment and is therefore not measured.

Molybdenum mass balance is defined as the difference in Mo input and Mo output. It will be calculated in a similar manner as Cu balance and includes the additional Mo intake from ALXN1840. The nominal amount of Mo contained in ALXN1840 will be used and is estimated as 3.33 mg in each 15 mg tablet per the following calculation: 95.96 g/mol (molecular weight of Mo)/ 432.54 g/mol (molecular weight of bis-choline tetrathiomolybdate) * 15 mg/tablet = 3.33 mg Mo. Mo mass balance will be calculated at steady state (Day 12 through Day 15) and over the entire Treatment Period (Day 1 through Day 30).

The average daily Cu and Mo balance, and/or change from Baseline in average daily Cu and Mo balance will be calculated using data from the following periods:

- Day -4 through Day -1 representing the Pre-dose Baseline Period (Cu/Mo balance)
- Days 4 through Day 15 representing the 30 mg/day Treatment Period (Cu balance for primary and secondary endpoints)
- Day 1 through Day 15 representing the ALXN1840 30 mg/day Treatment Period (Mo mass balance and Cu as exploratory analyses)
- Days 12 through Day 15 representing the Steady State Treatment Period (steady state Mo/Cu balance)
- Days 1 through Day 30 representing the entire Treatment and Post-treatment Period (total Mo and Cu balance)

As ALXN1840 is expected to increase Cu removal through fecal excretion, Cu in stool will be critical for determining Cu balance. Because stools can be irregular, assessment of Cu and Mo

balance will only include data up to the day of the final bowel movement. For example, if for the Day 1 through Day 15 collection period, the final bowel movement occurs on Day 14, average daily Cu balance for the Day 1 through Day 15 period will only include data averaged from Day 1 through Day 14 (and Day 15 data will be omitted).

In the case of the 30 mg/day Steady State Treatment Period for Mo balance, fecal data collected on Days 16 and 17 may be used if needed to support assessments for the 30 mg/day Mo steady state balance. Use of this fecal data (as needed) is consistent with an approximately 2-day gastrointestinal transit time.

In the case of bowel movement irregularity and to support assessment of Cu output over time, bowel movement Cu and Mo outputs may be averaged over the days between bowel movements (or start of study) to ensure an approximate value for each 24-hour period as needed for calculations. The 24-hour collection period is defined as relative to the first ALXN1840 dose administration.

7.3.1. Primary Analysis

The primary analysis will be performed using the FA Set. Additionally, the primary analysis will be performed on the PP Set. Change from Baseline in average daily Cu balance over Days 4 to 15 will be summarized using descriptive statistics based on data as observed. The 95% confidence limits for the mean change from Baseline will be provided.

7.3.1.1. Handling of Dropouts or Missing Data

Participants who prematurely discontinue from the study will be included up to the time of discontinuation.

7.3.1.2. Subgroup Analysis

There is no planned subgroup analysis.

7.3.1.3. Multicenter Studies

Not applicable.

7.3.1.4. Hypothesis Testing and Significance Level

Not applicable.

7.3.1.5. Sensitivity Analyses

There are no planned sensitivity analyses.

7.3.2. Secondary Analyses

Secondary analyses will be performed using the FA Set. The secondary continuous endpoints (Cu balance, Mo balance, urinary excretion, etc.) will be analyzed using the same methods described for the primary analysis. The periods of interest described in Section 7.3 will be utilized as appropriate. The daily Cu and Mo balances for each participant will be plotted, as will the mean daily Cu and Mo balances.

7.3.3. Exploratory Analyses

The exploratory endpoint analyses will be conducted on the FA Set. The exploratory endpoints will be analyzed in the same manner as the primary endpoint. Additionally, plasma Cu:Mo ratio and Cu:Mo ratio in urine and feces will be examined. The ratios will be derived at the participant level daily and then summarized. The periods of interest described in Section 7.3 will be utilized as appropriate.

To improve the understanding of the effects of ALXN1840 treatment duration, individual periods may be sub-segmented. For example, Day 1 through Day 15 may be divided into Day 1 through Day 5, Day 6 through Day 10, and Day 11 through 15 to assess Cu output early following treatment, in the middle of the Treatment Period and at the end of the Treatment Period.

7.4. Safety Analyses

All safety analyses will be made on the Safety Set.

Safety analyses will include all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics.

No inferential statistical analyses are planned for the safety parameters of this study.

7.4.1. Study Duration, Treatment Compliance, and Exposure

Study duration will be summarized for all enrolled participants by group and overall. Study duration is defined as the time from first dose to the EOS or study discontinuation date (whichever occurs first) + 1.

Compliance to the study treatment regimen will be determined as the days taken / the days expected to be taken during the treatment period x 100. Treatment compliance will be summarized using descriptive statistics by group. If a patient discontinues prematurely from the study, his or her compliance will be based on the period up to the point of discontinuation from the study. Compliance will also be summarized using counts and percentages by compliance category (i.e., ≥ 100% compliance, 80 to <100% compliance, 60 to <80% compliance, etc.).

Exposure will be summarized for the Safety Set by group and overall. The duration (days) of exposure to treatment will be calculated as date of last exposure to treatment – date of first dose + 1. The actual duration of treatment will be calculated as the exposure period – number of days on which treatment was temporarily stopped. The duration of exposure, average daily dose (mg), minimum daily dose (mg) and maximum daily dose (mg) will be summarized using descriptive statistics. A supportive listing will also be provided.

7.4.2. Adverse Events

The verbatim terms as reported in the CRF by Investigators to identify AEs will be coded using the MedDRA, Version 22.0 or higher and summarized by primary SOC and PT.

Adverse event toxicity will be evaluated using the NCI CTCAE Version 5.0 (published 27 Nov 2017).

Adverse event causality is determined by the Investigator using the following assessment categories: unrelated, or related.

Treatment-emergent AEs are defined as those AEs with onset on or after the first dose of treatment (ie, study drug). Events reported with a partial onset date (eg, month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

7.4.2.1. Overall Summary of Adverse Events

An overall summary of TEAEs will be presented, including number of events and number and percentage of participants experiencing AEs. Percentage will be calculated as n/N*100, where n is the number of participants with events and N is the number of participants in the Safety Set. The summary will include categories indicating how many events are TEAEs, treatment-emergent SAEs, and treatment-emergent non-SAEs. Within TEAEs, the following subcategories will also be summarized:

- Toxicity of TEAEs (Grade 1 through Grade 5)
- Related TEAEs (not related, related)
- TEAEs leading to withdrawal of study drug
- TEAEs leading to withdrawal from the study
- TEAEs leading to death

A summary of events (E) and number of participants with events (n, %) for pre-treatment adverse events (PTAEs) will also be included with its relevant subcategories.

A listing of all TEAEs by participant will be presented. Separate listings will be produced for SAEs, AEs leading to study drug withdrawal, AEs resulting in death, AEs leading to withdrawal from the study and PTAEs.

7.4.2.2. Adverse Events and Serious Adverse Events by System Organ Class and Preferred Term

The number of TEAEs and the number and percentage of participants with events will be presented by SOC and PT. Participants are counted once in each SOC and PT. Percentages will be based on the Safety Set. The SOCs will be listed in alphabetical order and PTs within each SOC will be listed by descending frequency. If needed, PTs will also be ordered alphabetically.

Treatment-emergent SAEs, treatment-emergent non-SAEs, TEAEs leading to withdrawal of study drug, TEAEs leading to withdrawal from the study, TEAEs leading to death, and PTAEs will be summarized using the same approach.

7.4.2.3. Adverse Events s by System Organ Class

The number of TEAEs and the number and percentage of participants with events will be presented by SOC only. Participants are counted once in each SOC. Percentages will be based on the total number of treated participants in the treatment cohort.

7.4.2.4. Adverse Events by Preferred Term

The number of TEAEs and the number and percentage of participants with events will be presented by PT only. Participants are counted once for each PT. Percentages will be based on the total number of treated participants in the treatment cohort.

7.4.2.5. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Relationship

The number of TEAEs and the number and percentage of participants with events will be presented by SOC and PT as described in Section 7.4.2.2 by relationship (related, not related). If a participant has more than 1 occurrence of an AE, the strongest relationship to study drug will be used in the summary table. If relationship to study drug is missing, the AE will be assumed to be related. A similar analysis will be conducted for treatment-emergent SAEs.

The number of related TEAEs and the number and percentage of participants with related TEAEs will be summarized by SOC and PT, and separately by PT only. The same analyses will be produced for related treatment-emergent SAEs.

Lastly, the number of TEAEs by SOC, PT, and relationship, without taking into account the highest relationship, will be analyzed. A similar analysis will be conducted for treatment-emergent SAEs.

7.4.2.6. Adverse Events and Serious Adverse Events by System Organ Class, Preferred Term, and Toxicity

The number of TEAEs and the number and percentage of participants with events will be presented by SOC, PT and toxicity (ie, CTCAE grade). If a participant has more than 1 occurrence of an AE, the highest toxicity reported will be used. If toxicity is missing, the AE will be assumed to be Grade 3 (ie, severe). The number of TEAEs by SOC, PT, and toxicity, without taking into account the highest toxicity, will also be analyzed.

Additionally, a summary of related TEAEs by SOC, PT, and toxicity using the highest toxicity will be presented.

7.4.3. Other Safety

7.4.3.1. Analyses for Laboratory Tests

Actual values and changes from treatment Baseline (eg, chemistry, blood cell count with differential, and urinalysis) will be summarized descriptively for participants with available data for each laboratory parameter by group and overall. Missing laboratory data will not be imputed and only scheduled assessments will be included in by-visit summaries. All data, including that which is only collected at Screening, will be included in data listings. Laboratory measurements will be listed separately by participant, laboratory test, unit, and visit.

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (ie, below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Contingency tables will be presented for each laboratory parameter to summarize the shift from the Baseline category to all

visits and to the worst post-Baseline measurement, defined as the value numerically farthest outside of the normal range across all post-Baseline visits through the end of the study.

Summary results for shift will include the count and percentage of participants within each shift category by scheduled visit. Laboratory values outside the normal range will also be summarized and assessed for trends indicating a safety signal. Additionally, a summary and listing of liver enzyme elevation will be presented and an evaluation of drug-induced serious hepatotoxicity plot will be created.

7.4.3.2. Vital Signs

Changes from Baseline in vital signs (blood pressure, heart rate, respiratory rate, and body temperature) at each visit will be summarized descriptively by group and overall. Missing vital signs data will not be imputed and only scheduled assessments will be summarized in tables; unscheduled assessments will be presented in data listings. A listing of vital signs will be presented by participant, vital sign, and visit.

7.4.3.3. Physical Examination

Abnormal physical examination results will be tabulated by study visit and body system. Physical examination data (including height and weight) will also be listed by scheduled visit.

7.4.3.4. Electrocardiogram

All ECG data will be fully listed and changes from Baseline in ECG data (heart rate, PR interval, RR interval, QRS duration, QT interval) will also be summarized descriptively by scheduled visit.

All QT intervals will be corrected for heart rate according to Fridericia ($QTcF = QT/(RR^{1/3})$). At each time point, the number and percentage of participants falling into the following categories according to the International Conference on Harmonization (ICH) E14 Guidelines will be presented:

- QTc actual values: ≤450 ms, >450 to ≤480 ms, >480 to ≤500 ms, and >500 ms
- QTc increases from Baseline of >30 msec and >60 msec

Changes from Baseline in QTc will also be summarized. Further, ECG data will be classified by the Investigator as “normal,” “abnormal, not clinically significant,” “abnormal, clinically significant” or “indeterminate” at each timepoint assessed. Summary results will include the count and percentage of participants within each category at each visit.

7.5. Pharmacokinetic and Pharmacodynamic Analyses

For PK and PD endpoints, analyses will be performed using the PK/PD Analysis Set.

7.5.1. Pharmacokinetic Concentration Analyses

Plasma concentrations of total Mo and PUF Mo (as surrogate measures of ALXN1840 PK) and time data will be presented in a data listing by participant. Plasma concentration data will be summarized separately by analyte, day and time point using the following descriptive statistics: number of participants, arithmetic mean, SD, coefficient of variation (CV), geometric mean

(GM), GMCV, median, minimum, and maximum. When calculating the GM, values of 0 will be discarded. For summary statistic calculations, plasma concentrations values below the lower limit of quantification (LLOQ) will be set to the LLOQ.

Mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual plasma concentration versus actual time profiles will be presented similarly. The time to reach steady-state will be graphically assessed by plotting mean plasma trough (predose) concentration observed at the start of the dosing interval (C_{trough}) versus study day in both linear and semilogarithmic scales. Additionally, time to steady state will be evaluated using stepwise testing for linear trend.

7.5.2. Pharmacodynamic Concentration Analyses

Individual ALXN1840 PD and biomarkers, assessed as plasma total Cu (PD), toxic Cu measured as plasma PUF Cu (PD), LBC (PD), NCC/non-ceruloplasmin-bound Cu concentration corrected for the amount of Cu bound to the Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration ($NCC_{corrected}$) (PD), and Cp (biomarker) and CpC (biomarker) concentration-time data (including measured, absolute change from Baseline and percent change from Baseline) will be listed by participant.

The PD and biomarker concentration (measured, absolute change from Baseline and percent change from Baseline) data will be summarized separately by analyte, day and time point using the following descriptive statistics: number of participants, arithmetic mean, SD, CV, GM, GMCV, median, minimum, and maximum. When calculating the GM, values of 0 will be discarded. For PD and biomarker summary statistic calculations, concentrations below the LLOQ will be set to the LLOQ.

Mean PD and biomarker concentration (measured, absolute change from Baseline and percent change from Baseline) versus scheduled time profiles will be presented in figures on linear scales. Individual PD and biomarker concentration (measured, absolute change from Baseline and percent change from Baseline) versus actual time profiles will be presented similarly.

7.5.3. Pharmacokinetic Parameter Analyses

The following plasma PK parameters, as data permit, will be calculated for total Mo and PUF Mo on Day 1 and Day 15 using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher, or SAS Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina), as applicable. Calculations will be based on the actual sampling times relative to the actual reference ALXN1840 dosing times recorded during the study.

- Time delay between the time of dosing and time of appearance of Mo concentration (T_{lag}) in plasma (Day 1 and Day 15)
- Maximum observed concentration (C_{max}) (Day 1 and Day 15)
- Time to maximum concentration (T_{max}) (Day 1 and Day 15)
- Trough (predose) concentration observed at the start of the dosing interval (C_{trough})
- Time of last quantifiable concentration (T_{last}) (Day 1 and Day 15)

- Observed concentration at the end of the dosing interval (C_τ, where τ = 24 h) (Day 1 and Day 15)
- Area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_t) (Day 1 and Day 15)
- AUC from time 0 to infinity (AUC_∞) (Day 1 only)
- AUC over the dosing interval (AUC_{tau}) (Day 1 and Day 15)
- Apparent terminal-phase elimination rate constant (λ_z) (Day 1 and Day 15)
- Terminal elimination half-life ($t_{½}$) (Day 1 and Day 15)
- Apparent total body clearance (CL/F) (Day 1 and Day 15)
- Apparent volume of distribution (V_d/F) (Day 1 and Day 15)
- Accumulation ratio (AR) calculated as C_{max}, C_{trough}, and AUC after repeat dosing on Day 15 divided by those after initial dosing on Day 1:
  - $C_{max,Day15}/C_{max,Day1}$
  - $C_{trough,Day15}/C_{trough,Day1}$
  - $AUC_{tau,Day15}/AUC_{tau,Day1}$

Additional plasma PK parameters may be calculated if deemed appropriate.

For the PK analysis, below the limit of quantification (BLQ) values prior to the first measurable concentration will be set to zero with the rest of all other BLQ values treated as missing

Pharmacokinetic parameters derived from plasma concentrations of total Mo and PUF Mo will be presented in data listings and summarized by analyte and day using the following descriptive statistics: number of participants, arithmetic mean, SD, arithmetic CV, GM, GMCV, median, minimum, and maximum.

7.5.4. Pharmacodynamic Parameter Analyses

The following plasma PD parameters, as data permit, will be calculated for total Cu, PUF Cu, and LBC on Day 1 and Day 15 using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher, or SAS Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina), as applicable. Calculations will be based on the actual sampling times relative to the actual reference ALXN1840 dosing times recorded during the study.

- Maximum observed effect after dosing (CE_{max}) (Day 1 and Day 15)
- Time after dosing at which the maximum effect was observed (TE_{max}) (Day 1 and Day 15)
- Time after dosing at which the last quantifiable concentration was observed (TE_{last}) (Day 1 and Day 15)
- Trough (predose) effect concentration observed at the start of the dosing interval (C_{trough})

- Area under the effect versus time curve (AUEC) from the start of dose administration to the last observed quantifiable concentration ($AUEC_t$) (Day 1 and Day 15)

Additional plasma PD parameters may be calculated if deemed appropriate.

For the PD parameter estimation, plasma concentrations below the LLOQ will be set to the LLOQ.

Pharmacodynamic parameters derived from plasma concentrations of total Cu, PUF Cu, and LBC will be presented in data listings and summarized by analyte and day using the following descriptive statistics: number of participants, arithmetic mean, SD, arithmetic CV, GM, GMCV, median, minimum, and maximum.

8. REFERENCES

Camilleri M, Brown ML, Malagelada JR. Relationship between impaired gastric emptying and abnormal gastrointestinal motility. Gastroenterology. 1986;91(1):94-99.

Metcalf AM, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. Gastroenterology. 1987;92(1):40-47.

NCI, 2017. National Cancer Institute Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH), Department of Health and Human Services (DHHS). Common Terminology Criteria for Adverse Events V5.0 (CTCAE). Published: November 27, 2017. Available online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. The quick reference guide is available online at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Strickland GT, Blackwell RQ, Watten RH. Metabolic studies in Wilson's disease. Evaluation of efficacy of chelation therapy in respect to copper balance. Am J Med. 1971;51(1):31-40.

Weaver LT, Steiner H. The bowel habit of young children. Arch Dis Child. 1984;59(7):649-652.

9. APPENDICES

9.1. Sample Size, Power, and Randomization

The study sample size is not based on null hypothesis significance testing. A sample size of 13 participants was selected based on convention for this type of study (Strickland, 1971). To accommodate a 25% dropout rate, approximately 17 participants will be enrolled and will receive study drug to achieve 13 evaluable participants who complete the study.

Randomization is not applicable. This is an open-label study in which all participants are expected to receive the same dose of ALXN1840.

9.2. Technical Specifications for Derived Variables

9.2.1. Adverse Events

The analysis of AEs is described in detail in Section 7.4.2.

Treatment-emergent AEs are events with start dates and start times on or after the date and time of the first study drug dose. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study drug dose, then the AE is treatment-emergent; else,
- If the start year is the same as the year of the first study drug dose and
  - the start month is missing, then the AE is treatment-emergent; else if
  - the start month is present and is the same or after the month of the first study drug dose, then the AE is treatment-emergent; else,
- If the start date is completely missing, then the AE is treatment-emergent.

All other AEs are considered PTAEs (ie, AEs with partial or complete start dates before first study drug dose).

9.2.2. Age and Dates

Age will be presented as the number of years between date of birth and the reference date. The following age in Table 2 may be computed, with reference date indicated.

Table 2: Age and Reference Date

Age	Reference Date
• Age at enrollment	• Date of informed consent

The following formula should be followed for calculation of age if needed:

Age (year) = FLOOR(reference date – date of birth)/365.25

where FLOOR( ) function returns the integer part of the result.

In cases where only the month and year are provided for a date, the day for the date will be imputed as 15. Missing month will be imputed as June. In cases where the day is observed but

the month is missing, the date will be imputed as June 15. In instances when the imputed reference date is earlier than the birth date, the birth date will be used as the reference date.

9.2.3. Analysis Relative Day

Analysis relative day is the day relative to the first dosing day. It will be calculated as: analysis date – first dose date + 1 if analysis date is after the first dose date, or else as: first dose date – analysis date.

9.2.4. Baseline Value

The Baseline value is defined as the last non-missing value collected on or prior to first dose.

9.2.5. Body Mass Index

The BMI is derived as follows: weight (kg) / [height (cm) / 100]^2

9.2.6. Change From Baseline

Change from Baseline will be calculated as: post-Baseline assessment value – Baseline assessment value when both values are not missing.

Percent change from Baseline is calculated as (change from Baseline/Baseline result * 100).

If either the Baseline or the post-Baseline result is missing, the change from Baseline and/or percentage change from Baseline is set to missing. Additionally, if the Baseline is 0, the percentage change from Baseline will be missing.

9.2.7. Medications and Therapies

Medication/therapies with administration dates and times on or after the date and time of the first study drug dose are considered concomitant. If the start date of a medication or therapy is partially or completely missing and the end (stop) date and time of the medication/therapy does not indicate that it occurred prior to first dose, then the determination of concomitant status will be based on the following:

If the start year is after the year of the first study drug dose, then the medication/therapy is concomitant; else, if the start year is the same as the year of the first study drug dose and the start month is missing, then the medication/therapy is concomitant; else if the start month is present and is the same or after the month of the first study drug dose, then the medication/therapy is concomitant; else, if the start date is completely missing, then the medication/therapy is concomitant.

All other medications/therapies are considered prior medications/therapies and could occur from the 14 days prior to study enrollment through the Screening Period and prior to the first dose.

9.2.8. Visit Windowing

In analysis of data summarized by study visit, all data collection will be reassigned a study visit where data is scheduled for collection based on the actual days relative to Baseline. All visits will be assigned a target study day. Baseline will have a target study day of 1. For each assessment, the post-Baseline period will be divided up using the scheduled visit's target day.

The lower bound of each visit interval will be evaluated as the mid-point between the target day and the previous visit's target day in the following manner: study day interval lower bound = ceiling(target study day – ((target study day – last target study day)/2)). Table 3 shows an example of visit windowing that will be used to summarize by-visit vital sign data. Other data will be summarized similarly in accordance to their SoA (Protocol Table 1).

Table 3: Visit Windows Used to Summarize By-visit Vital Signs Data

Scheduled Visit	Target Study Day	Study Day Interval
Baseline	1	Last measurement on or prior to first dose of study drug
Day 2	2	2 to 3
Day 5	5	4 to 6
Day 8	8	7 to 9
Day 11	11	10 to 12
Day 14	14	13 to 14
Day 15	15	15+

If more than 1 value is mapped to the same scheduled visit, the closer of those values will be considered for summarization. If multiple records exist with the same distance from the target study day, the last occurrence will be used. Visit windows are intended to be contiguous such that all data collected at all post-Baseline visits, whether scheduled or unscheduled, will map to one of the visits.

The visit displayed on data listings will be reflective of the scheduled visit label as reported on the CRF. Study days relative to Baseline will be displayed for each visit so it is apparent which visit the data may have been reassigned to in the summaries.

9.3. Additional Details on Statistical Methods

Not applicable.