STATISTICAL ANALYSIS PLAN: INDV-2000-102 Parts I & II

Protocol Title: A Phase I Double-Blind, Placebo-Controlled Randomized Study to Assess Repeated Doses of INDV-2000 (C4X_3256) up to 28 Days in Healthy Volunteers, and an Open-Label Study of INDV-2000 up to 11 Days in Treatment Seeking Individuals with Opioid Use Disorder

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Statistical Analysis Plan

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Protocol Number:	INDV-2000-102
Compound Number:	INDV-2000 (C4X_3256)
Sponsor Name:	Indivior
Legal Registered Address:	10710 Midlothian Turnpike, Suite 125 North Chesterfield, VA 23235 USA
IND Number:	145881
Protocol Version:	Amendment 3.0, Version 4.0
Date:	28 July 2022

Statistical Analysis Plan Approval

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1. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study INDV-2000-102 Parts I and II and is based on Protocol Amendment 3/28 July 2022 (Version 4.0). This SAP supersedes the statistical considerations stated in the protocol; any differences are identified in Appendix 2 of this document. However, major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Post hoc or unplanned analyses not specified in the SAP will be documented in the clinical study report (CSR).

VERSION HISTORY

Table 1 SAP Version History Summary

SAP Version	SAP Finalization Date	Associated Protocol Amendment	Protocol Approval Date	Change	Rationale
1.0	06Oct2022	Amendment 3.0, Version 4.0	28Jul2022	Not Applicable	Original version

1.1. Objectives and Endpoints

Each study objective is presented in Table 2 with associated estimands. Intercurrent events occur after treatment starts and either preclude the observation of an endpoint or affect its interpretation. For the intercurrent event of study discontinuation, the principal stratum strategy will be used for PK endpoints in that only subjects with an adequate amount of PK data will be included in the PK population; for all other endpoints, the while-on-treatment strategy will be used since data will be collected only up to end of study (EOS) or study discontinuation. Other potential intercurrent events in this study are prohibited medications and lifestyle restrictions detailed in protocol sections 9.6.2 and 9.6.3, respectively. Possible strategies for these intercurrent events are treatment policy (intercurrent event is ignored), while on treatment (data collected after the event is ignored), and principal stratum for PK endpoints (subject is excluded from the PK population), to be decided by the sponsor on a case-by-case basis.

Table 2 Study Objectives and Estimands

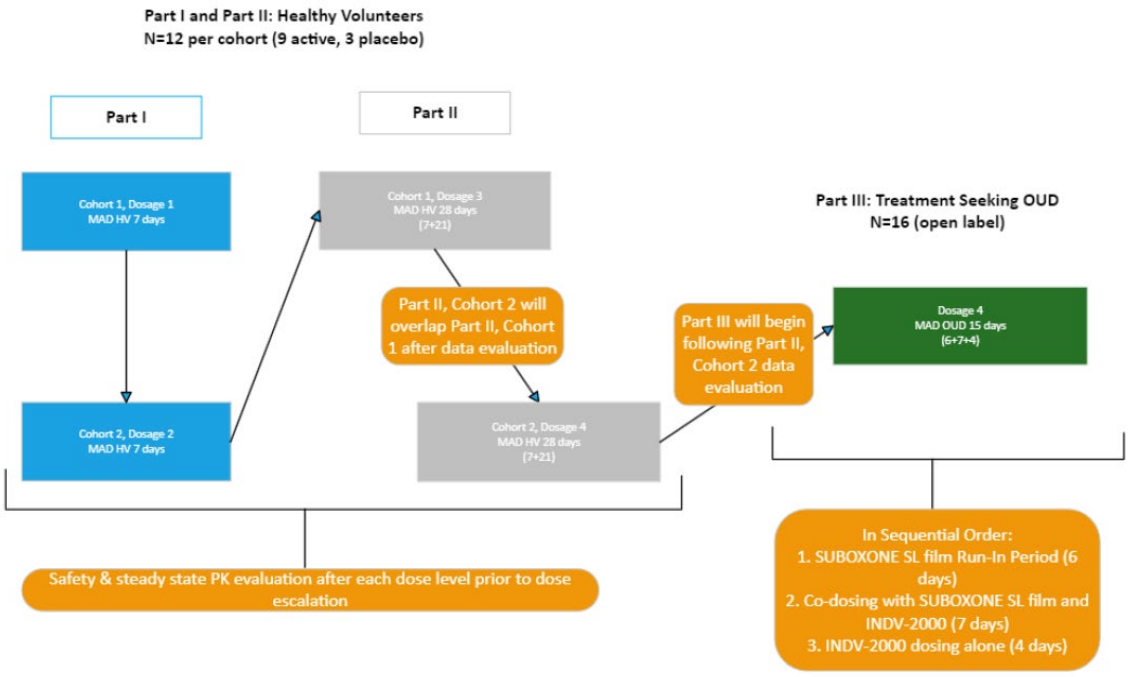
		Estimand		
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**Population-Level Summary**
Primary Objective Assess safety and tolerability of INDV-2000 following repeated doses of INDV-2000 in healthy volunteers**.**				
Adverse Events (AEs)	Primary	Incidence, severity, and relatedness of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and events leading to study discontinuation or death.	Safety	Categorical descriptive
Secondary Objective Characterize the pharmacokinetic (PK) profile following multiple doses of INDV-2000.				
PK	Secondary	INDV-2000 maximum plasma concentration (C_{max}) following dosing on Days 1 and 7 for Part I and on Days 1, 7 and 28 for Part II	PK	Numeric descriptive
		INDV-2000 time of maximum plasma concentration (T_{max}) following dosing on Days 1 and 7 for Part I and on Days 1, 7 and 28 for Part II	PK	Medians, ranges
		INDV-2000 area under the plasma concentration-time curve ($AUC_{0-\tau}$) following dosing on Days 1 and 7 for Part I and on Days 1, 7 and 28 for Part II (τ = 12h for BID dosing and 24h for QD dosing)	PK	Numeric descriptive
Exploratory Objectives				
[redacted]				

		Estimand		
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**Population-Level Summary**
[redacted]				

1.2. Study Design

This is a Phase I study to assess repeated doses of INDV-2000 in healthy volunteers and in treatment-seeking individuals with OUD. The study will be conducted in three parts, as depicted in Figure 1. This SAP is for Parts I and II only.

Figure 1. Study Schematic



Key features of the study design are described below.

- Parts I and II are randomized, double-blind, placebo-controlled, multiple ascending dose studies, with each part consisting of two INDV-2000 dosing cohorts.
- In each of Parts I and II, 12 healthy volunteers in each cohort (48 subject total) will be randomized to INDV-2000 or placebo in a 3:1 ratio using block size 4.
- Each part of the study will have a 28-day screening period. Total study duration per subject, from screening through the end-of-study (EOS) visit, will be approximately 42 days for Part I and 63 days for Part II.
- For male subjects, there will be a safety phone call 90 days after last dose to assess any new pain, swelling or nodular lesions in the scrotum.
- Safety and PK evaluations will be done after each cohort.

2. STATISTICAL HYPOTHESES

There will be no statistical inference in this study. All statistics will be descriptive only.

2.1. Multiplicity Adjustment

There will be no statistical inference in this study; therefore, there will be no need for multiplicity adjustment.

3. SAMPLE SIZE DETERMINATION

The sample size for each part of the study is not based on formal power calculations because the study is designed to provide preliminary descriptive assessments of the safety, tolerability and PK for INDV-2000. The sample sizes used are typical for studies of this nature and should be adequate to assess the parameters described.

4. POPULATIONS FOR ANALYSIS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population shown in Table 3 prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

Table 3 Analysis Populations

Population	Description
Screened	Subjects who signed informed consent.
Safety	Subjects who received at least one dose of investigational medicinal product (IMP). Subjects will be summarized according to the study treatment received.
PK	Subjects who received at least one dose of INDV-2000, have an adequate number of PK samples collected to derive any PK parameter, and have no protocol deviations that would significantly alter plasma concentration of INDV-2000.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Timing of Analyses

There will be a blinded review of the safety and PK data after completion of each cohort before dose escalation. The safety data review will be conducted by a Data Review and Safety Committee (DRSC). The Sponsor team may unblind after the dose escalation decision per cohort has been made. Database lock and final production of TFLs will occur after the completion of Part II.

5.1.2. Programming Environment

SAS® version 9.4 or higher (SAS Institute, Cary, North Carolina) will be used for statistical analyses and the production of Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) data sets as well as TFLs.

5.1.3. Reporting Conventions

Data will be listed and summarized separately for Parts I and II of the study. Data will be summarized by dosing cohort for active treatment and for placebo subjects pooled over both dosing cohorts. TFL tables of contents, mock-ups, and specifications are provided in a separate document from the SAP. The following reporting conventions will be followed:

- Treatment group names and order in tables and figures (if applicable) will be INDV-2000 xxx mg QD, INDV-2000 xxx mg BID, INDV-2000 Pooled, Placebo Pooled, and All Subjects [actual dose (xxx) is to be determined]. Some tables may omit the INDV-2000 Pooled and/or All Subjects groups.

- Tables and figures will present summaries/analyses by study visit and time point, as appropriate.

- Table column headers and figure legends will include subgroup sample sizes ("N = xx"). Sample sizes reported as part of descriptive statistics ("n") will be the number of non-missing observations.

- Listings will generally include unique subject identifier (including site identifier), assigned or actual treatment, study visit/time point, assessment or collection date/time, parameter, and observed value.

5.1.4. General Analysis Conventions

Categorical variables will be summarized using frequencies and percentages. Percentages will be reported to one decimal place.

Continuous variables will be summarized using descriptive statistics (e.g., n, mean, standard deviation (SD), distribution percentiles, range). The number of decimal places for minimums and maximums will be the same as the source data. The number of decimal places for means, medians, and interquartile ranges will be the same as the source data plus one, and the number of decimal places for measures of variance will be the same as the source data plus two. See Section 6.5 (Appendix 5) for summary statistics and precision specifications for PK data.

Data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.

5.1.5. Definitions

IMP: INDV-2000 or placebo

Screening Period: Informed consent to Day -1 Clinic Check-In.

End-of-Study (EOS): Early termination or completion of last scheduled visit.

Study Day 1: day of first dose of IMP administered in the clinical unit.

Study day:

- Study day = date of assessment – date of Study Day 1 + 1, for assessments on or after Study Day 1
- Study day = date of assessment – date of Study Day 1, for assessments before Study Day 1

Study time: time of assessment – time of first study drug administered in the clinical unit.

Duration:

- Duration in days = end date – start date + 1
- Duration in minutes = end time – start time. Durations will be adjusted for Daylight Saving Time, where applicable.

Baseline observation: for a given parameter for a given subject, the last observed value, including unscheduled and repeated assessments, before the first dose of IMP or planned first dose of IMP if IMP was not administered, unless otherwise specified (see Sections 5.6.3.2 and 5.6.3.3).

5.2. Study Conduct and Participant Disposition

Subject disposition summaries will include the number of subjects who were screened for Parts I and II, who were randomized, who were in each analysis population, and who completed the study. For percentages, the number of subjects screened will be the denominator for subjects randomized; the number of subjects randomized will be the denominator for the analysis populations and for subjects completing the study.

Reason for study discontinuation will be summarized by number and percentage of subjects for each reason reported; for the percentage, the number of subjects who discontinued will be the denominator.

Reason for screen failure will be summarized in a separate table by number and percentage of subjects for each reason reported; the denominator will be the number of screen failures.

5.3. Primary Endpoints Analysis

5.3.1. Definition of Endpoints

The primary endpoints are incidence of TEAEs, maximum severity TEAEs, TEAEs related to IMP, treatment-emergent serious adverse events (TESAEs), and TEAEs leading to study discontinuation or death.

5.3.2. Main Analytical Approach

Estimand strategy: While on treatment.

Analysis set: Safety (see Table 3).

Analysis methodology: Descriptive only.

Intercurrent events and missing data: AE data will no longer be collected on subjects who discontinue early from the study. See Section 6.6.3 (Appendix 6) for details on handling of missing AE information.

See Section 5.6.2 for details on AE summaries and listings.

5.4. Secondary Endpoints Analysis

5.4.1. Definition of Endpoints

The secondary endpoints are:

- INDV-2000 C_{max} following dosing on Days 1 and 7 (Part I) or on Days 1, 7, and 28 (Part II)
- INDV-2000 T_{max} following dosing on Days 1 and 7 (Part I) or on Days 1, 7, and 28 (Part II)
- INDV-2000 $AUC_{0-\tau}$ following dosing on Days 1 and 7 (Part I) or on Days 1, 7, and 28 (Part II)

5.4.2. Main Analytical Approach

Estimand strategy: Principal stratum.

Analysis set: PK (see Table 3).

Analysis methodology: Standard non-compartmental methods based on actual sampling times. Summaries will be descriptive only. See Section 6.4.1 (Appendix 4).

Intercurrent events and missing data: Subjects with intercurrent events may be excluded from the PK Population, to be decided by the sponsor on a case-by-case basis. See Section 6.6.1 (Appendix 6) for details on handling of missing data.

5.5. Exploratory Endpoints Analysis

5.5.1. Definition of Endpoints

[redacted]

5.5.2. Main Analytical Approach

[redacted]

5.6. Other Safety Analyses

5.6.1. Extent of Exposure and Treatment Compliance

IMP exposure will be summarized for the Safety Population as total number of doses, dose duration (days), percentage of expected number of doses (%), and number and percentage of subjects with number of doses less than 80% of expected. Expected number of doses for each part of the study is shown in Table 4. For Part II, percentage of expected number of doses and number and percentage of subjects with number of doses less than 80% of expected will be summarized both overall and separately for in-clinic vs. outpatient dosing; for outpatient dosing, this will be a measure of compliance since this is the only period of the study for which IMP is self-administered.

Table 4 Expected Number of IMP Doses by Study Part

Study Part	Expected Number of IMP Doses
Part I, Cohort 1	7
Part I, Cohort 2	14
Part II	55: 19 in-clinic, 36 outpatient

5.6.2. Adverse Events

A TEAE is an AE that started at or after first administration of IMP.

AEs will be coded to a System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). Additional details of the coding process, including the current version of the dictionary, are described in the Data Management Plan.

All AEs will be listed for individual subjects. Listings will include SOC, PT, and reported term; onset date and time, end date, and duration; treatment-emergence, severity, toxicity grade, seriousness and seriousness criteria; relationship to and action taken with IMP; whether concomitant treatment was given; outcome; and whether the AE resulted in study discontinuation. Duration (days) is calculated as the AE end date – the AE onset date +1; for ongoing AEs, the date of end of study participation will be used as the end date. Duration will be missing if either the start or end date is partially or completely missing. TESAEs, TEAEs leading to IMP discontinuation or interruption, and fatal TEAEs will be listed separately.

The incidence and number of all TEAEs, TESAEs, IMP-related TEAEs and TESAEs, severe TEAEs, TEAEs with grade 3 or higher toxicity grade, TEAEs leading to IMP discontinuation or interruption, and fatal TEAEs will be presented in an overall summary table.

TEAEs, TESAEs, IMP-related TEAEs and TESAEs will be summarized by MedDRA SOC and PT, each in descending order of frequency among all subjects within study part (then alphabetically in case of ties). TEAEs will also be summarized by maximum severity and by maximum toxicity grade within SOC and PT. If an AE is reported more than once by a subject within a SOC and/or PT, the maximum reported level of severity/toxicity will be used at each level of summation in the severity/toxicity summary table.

Incidence and number of TEAEs will also be summarized by PT only (ie, not SOC), sorted by descending frequency among all subjects (within study part).

Non-TEAEs are defined as AEs that started before first administration of IMP. Non-TEAEs will be summarized for randomized subjects.

See Section 6.6.3 (Appendix 6) for details on handling of missing AE information.

5.6.3. Additional Safety Assessments

5.6.3.1. Laboratory Data

Planned laboratory evaluations (Table 5) will be summarized by analysis visit as observed values and, for numeric values, changes from baseline. Normal/abnormal shifts from baseline will also be summarized. Abnormal laboratory evaluations will be listed separately. Laboratory evaluations done only at screening will be listed but not summarized. Reported values of clinical laboratory parameters that include qualifiers (ie, <, ≤, >, ≥) will be listed as reported but will be summarized without the qualifier.

Table 5 Planned Laboratory Evaluations

Haematology	**Serum Chemistry:**
Haematocrit	Albumin
Haemoglobin	Alkaline phosphatase
Mean corpuscular haemoglobin	Alanine aminotransferase (ALT)
Mean corpuscular haemoglobin concentration	Amylase
Mean corpuscular volume	Aspartate aminotransferase (AST)
Platelet count	Blood urea nitrogen
Red blood cell count	Calcium
White blood cell count with differential (absolute count)	Carbon dioxide
	Chloride
Urinalysis:	Creatinine
Appearance	Creatine kinase
Bilirubin	Gamma-glutamyl transferase
Colour	Glucose (non-fasting)
Glucose	Lactate dehydrogenase
Ketones	Lipase
Leucocyte esterase	Magnesium
Microscopic examination of sediment[a]	Phosphorus
Nitrite	Potassium
Occult blood	Sodium
pH	Total bilirubin
Protein	Direct bilirubin
Specific gravity	Total cholesterol
Urobilinogen	Total protein
	Triglycerides
Pregnancy:	
Serum hCG	**Urine Drug Screen (UDS):**
Urine hCG	Opioids
	Cocaine
Molecular	Amphetamines
PCR for COVID-19	Cannabinoids
	Barbiturates
Screening Only:	Benzodiazepines
FSH (as needed in post-menopausal females only)	Methamphetamine
Haemoglobin A1c	Phencyclidine
Hepatitis B surface Antigen	Ethanol
Hepatitis C Antibody	**In addition to the above, for Part III:**
HIV-1 and -2 antibodies	Fentanyl
Prothrombin Time with INR	Oxycodone
PTT	

Anti-HIV = human immunodeficiency virus antibodies; hCG = human chorionic gonadotropin; INR = international normalized ratio; and PTT = partial thromboplastin time.

[a] Microscopic examination of sediment will be performed only if the results of the urinalysis evaluation are positive (microscopic examination may include but is not limited to White Blood Cell count, Red Blood Cell count, casts and crystals).

5.6.3.2. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature) will be summarized as observed values and changes from baseline by analysis visit and time point. For blood pressure, the mean of triplicate measurements will be used for baseline, if available.

5.6.3.3. Electrocardiogram (ECG) Data

Numeric 12-lead ECG parameters [heart rate, PR interval, QRS duration, QT interval, Fridericia's corrected QT interval (QTcF)] will be summarized as observed values and changes from baseline by analysis visit and time point; the mean of triplicate measurements will be used for baseline, if available. ECG interpretation (normal, abnormal not clinically significant, abnormal clinically significant) will be summarized by visit and time point as shifts from baseline, with baseline interpretation defined as the consensus among triplicate assessments, if available; if there is no consensus, the Sponsor will be notified and will provide a baseline interpretation based on a review of the data.

5.6.3.4. Columbia-Suicide Severity Rating Scale (C-SSRS)

The composite endpoints Suicidal Ideation and Suicidal Behavior will be derived from the following 10 binary C-SSRS questions, reordered from the actual scale to facilitate the derivation:

Question 1	Wish to be Dead
Question 2	Non-specific Active Suicidal Thoughts
Question 3	Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Question 4	Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Question 5	Active Suicidal Ideation with Specific Plan and Intent
Question 6	Preparatory Acts or Behavior
Question 7	Aborted Attempt
Question 8	Interrupted Attempt
Question 9	Actual Attempt (non-fatal)
Question 10	Completed Suicide

Suicidal Ideation is derived as "yes" if any of Question 1-5 has a "yes" response. Suicidal Behavior is derived as "yes" if any of Question 6-10 has a "yes" response. If there are zero "yes" responses and at least one question has a missing response, the derived composite will be missing. Suicidal Ideation and Suicidal Behavior will be summarized as categorical variables by analysis visit.

[redacted]

5.7. Other Analyses

5.7.1. Demographic and Baseline Characteristics

Demographic and other baseline characteristics will be summarized separately for the safety and PK populations, if different. A summary will also be done for screen failures. Parameters to be summarized will be age, sex, race, ethnicity, fertility status, height/weight/body mass index, and substance use (alcohol, nicotine, xanthine/caffeine) status (never/current/former).

5.7.2. Medical History

Relevant medical history will be coded using MedDRA (refer to the Data Management Plan) and will be listed for the safety population.

5.7.3. Prior and Concomitant Medications and Therapies

Medications and therapies will be collected from screening through EOS and will be coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug Dictionary (WHO-DD). Additional details of the coding process, including the current version of the dictionary, are described in the Data Management Plan. Prior medications and therapies will be medications/therapies that ended before first administration of IMP or were taken by subjects who did not start IMP. All other medications and therapies will be considered concomitant.

Prior medications and therapies will be summarized for randomized subjects. Concomitant medications will be summarized for the safety population. The summary of incidence (number and percentage of subjects reporting the medication/therapy at least once) will be sorted alphabetically by therapeutic class (ATC level 2) and standardized medication/therapy name.

See Section 6.6.4 (Appendix 6) for details on handling missing information on medications and therapies.

5.7.4. Protocol Deviations

Protocol deviations will be identified and documented prior to database lock and will be summarized by category (eg, prohibited medication, out-of-window assessment) and type (eg, major, minor), per the Protocol Deviation Plan for the study, for randomized subjects. Deviations that occur in subjects who were not randomized, if any, will be summarized separately. All protocol deviations will be listed.

5.8. Interim Analyses

Not applicable.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	Anatomic Therapeutic Chemical
$AUC_{0-\tau}$	area under the curve from 0 to τ, where τ =12h for BID dosing and 24h for QD dosing
BLQ	below limit of quantitation
C-SSRS	Columbia-Suicide Severity Rating Scale
C_{max}	maximum plasma concentration
CRF	Case Report Form
CSR	Clinical Study Report
[redacted]	[redacted]
DRSC	Data Review and Safety Committee
ECG	electrocardiogram
EOS	end of study
IMP	investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
OUD	opioid use disorder
PK	Pharmacokinetic
PT	Preferred Term
QTcF	Fridericia's corrected QT interval
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFLs	tables, figures, and listings
T_{max}	time of maximum plasma concentration
[redacted]	[redacted]
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2: Changes to Protocol-Planned Analyses

The following are changes from the protocol that are in the SAP:

Protocol:	**SAP:**
	Added Screened analysis population.
AUC endpoint described as $AUC_{0\text{-}12h \text{ or } 0\text{-}24h}$	AUC endpoint described as $AUC_{0\text{-}\tau}$, where τ = 12h for BID dosing and 24h for QD dosing.

[redacted]

6.3. Appendix 3: Definition and Use of Visit Windows in Reporting

No windowing will be used for summaries. Analysis visits will be visits denoted in the CRF. If a participant has more than 1 assessment for a given visit, the most recent non-missing assessment will be used for summaries.

6.4. Appendix 4: Endpoint Derivations

6.4.1. Pharmacokinetic Endpoints

[redacted]

6.5. Appendix 5: Statistical Methodology Details

Statistical programming will be done using SAS version 9.4 (or later) on a Windows 10 Enterprise (or later) operating system. Plasma PK parameters will be calculated using Phoenix™ WinNonlin® (Version 8.3.4, Certara, LP).

6.5.1. PK Analysis

6.5.1.1. Concentration

[redacted]

6.5.1.2. PK Parameters

6.6. Appendix 6: Methods to Manage Missing Data

6.6.1. BLQ PK Concentrations

Concentration values that are reported as BLQ will be presented as “BLQ” in concentration listings, replaced by 0 for summary statistic calculations and linear-scale plots of concentrations, and excluded from semi-logarithmic-scale plots of concentrations.

For derivations of PK plasma parameters, all concentrations that are BLQ prior to the first measurable concentration will be set to zero. BLQ values that are between measurable concentrations will be set to missing. Measurable concentrations between 2 BLQ values will be set to missing. If two or more consecutive BLQ concentrations are followed by quantifiable concentrations, these quantified values will be set to missing. If a BLQ concentration is followed by a quantifiable concentration, and the quantifiable concentration is then followed by two or more consecutive BLQ concentrations, the quantifiable concentration will be set to missing. The BLQ values following the last quantifiable time points will be set to missing. No concentration estimates will be imputed for missing sample values.

6.6.2. Exposure

Missing IMP Dosing Information

All efforts should be made to obtain missing IMP dosing information from the investigator. If data are still missing after all efforts, then total exposure will be missing and the dose will be considered missing for the calculation of compliance.

Missing Last Date of IMP Exposure

All efforts should be made to obtain missing last date of IMP exposure from the investigator. If the last date of exposure is still missing after all efforts, then the last available dosing record date may be used as the last IMP exposure date for the calculation of exposure duration.

6.6.3. AEs

Missing AE Severity

Missing AE severity must be queried until resolution. In the unlikely event that resolution is not possible, missing severity will be imputed as “severe” in summaries.

Missing AE Relationship to IMP

Missing relationship to IMP for a TEAE must be queried until resolution. In the unlikely event that resolution is not possible, missing relationship will be imputed as “related” in summaries.

Missing AE Seriousness

Missing AE seriousness must be queried until resolution. Seriousness cannot be imputed as “serious” since doing so would affect the reconciliation between the trial database and the SAE registry.

Missing AE Toxicity Grade

Missing AE toxicity grade must be queried until resolution, where applicable. There will be no imputation for missing toxicity.

Missing AE Start Date/Time Information

Note: partial times will not be recorded in the CRF.

For the Safety Population, an AE will be considered treatment emergent under the following conditions:

- Missing start year, month, day, time unless it can be deduced from non-missing components of AE end date that the AE ended before first IMP.

- Missing start month, day, time if start year is equal to or after year of first IMP, unless it can be deduced from non-missing components of AE end date that AE ended before first IMP.

- Missing start day and time if start year is after year of first IMP or if start year is equal to year of first IMP and month is equal to or after month of first IMP, unless AE end date is before date of first IMP.

- Missing start time if start date is on or after date of first IMP.

6.6.4. Medications and Therapies

Missing End Date/Time Information

Note: partial times will not be recorded in the CRF.

Prior vs. concomitant status will be assigned as follows:

Non-missing end date, missing end time

- If end date is before date of first IMP, medication/therapy is prior.
- If end date is equal to or after date of first IMP, medication/therapy is concomitant.

Non-missing end year and month, missing end day

- If end year is before year of first IMP, medication/therapy is prior.
- If end year is equal to year of first IMP and end month is before month of first IMP, medication/therapy is prior.
- If end year is equal to year of first IMP and end month is equal to or after month of first IMP, medication/therapy is concomitant.
- If end year is after year of first IMP, medication/therapy is concomitant.

Non-missing end year, missing end month and day

- If end year is before year of first IMP, medication/therapy is prior.
- If end year is equal to or after year of first IMP, medication/therapy is concomitant.

Missing end year, month, and day

- Medication/therapy is concomitant if subject was dosed; otherwise, medication/therapy is prior.

6.7. Appendix 7: Data Set Descriptions

Trial data sets will consist of CRF exports and external data files. External files may be used for protocol deviations and data from the central laboratory, for example.

7. REFERENCES

None.