STATISTICAL ANALYSIS PLAN: INDV-2000-104

Protocol Title: An Open Label, Fixed-sequence Study to Evaluate the Potential CYP3A4 Induction Effect of INDV-2000 using Oral Midazolam as a Probe in Healthy Adults Participants

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Statistical Analysis Plan

Protocol Title:	An Open Label, Fixed-sequence Study to Evaluate the Potential CYP3A4 Induction Effect of INDV-2000 using Oral Midazolam as a Probe in Healthy Adults Participants
Protocol Number:	INDV-2000-104
Compound Number:	INDV-2000
Sponsor Name:	Indivior
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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-2000-104 and is based on Amendment 1 of the protocol dated 10 Apr 2023. This SAP supersedes the statistical considerations stated in the protocol; any differences are identified in Section 6.2 (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 Version	Protocol Approval Date	Change	Rationale
1.0	22May2023	Amendment 1	10Apr2023	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 affects its interpretation. For the intercurrent event of study discontinuation, the principal stratum strategy will be used for pharmacokinetic (PK) endpoints in that only subjects with an adequate amount of PK data will be included in the PK Analysis Set (Table 3); 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 6.9 and 5.3, respectively. Possible strategies for these intercurrent events are treatment policy (intercurrent event is ignored), while on treatment (data collected after the event would be ignored), and principal stratum for PK endpoints (subject would be excluded from the PK Analysis Set), 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**	**Pop-ulation**	**Population-Level Summary**
Primary Objective To determine changes in primary PK parameters (maximal and overall plasma exposure) of midazolam and 1-hydroxymidazolam following repeated oral doses of INDV-2000.				
PK	Primary	Midazolam maximum plasma concentration (C_{max}) following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15.	PK	Geometric mean ratios (Day 15/Day 1) with 90% confidence intervals (CIs)
		Midazolam area under the plasma concentration-time curve from 0 to infinity ($AUC_{0-\infty}$) following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15.	PK	Geometric mean ratios (Day 15/Day 1) with 90% CIs
		Midazolam area under the plasma concentration-time curve from dosing to the last measured concentration (AUC_{last}) following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15.	PK	Geometric mean ratios (Day 15/Day 1) with 90% CIs
		1-hydroxymidazolam C_{max} following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15.	PK	Geometric mean ratios (Day 15/Day 1) with 90% CIs
		1-hydroxymidazolam $AUC_{0-\infty}$ following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15.	PK	Geometric mean ratios (Day 15/Day 1) with 90% CIs
		1-hydroxymidazolam AUC_{last} following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15.	PK	Geometric mean ratios (Day 15/Day 1) with 90% CIs
Secondary Objective To assess the safety and tolerability of repeated oral doses of INDV-2000 in combination with midazolam as determined by adverse event (AE) reporting.				
AEs	Secondary	Incidence, seriousness, severity, and relatedness of treatment-emergent AEs (TEAEs).	Safety	Categorical descriptive

Tertiary/Exploratory Objectives

[redacted]

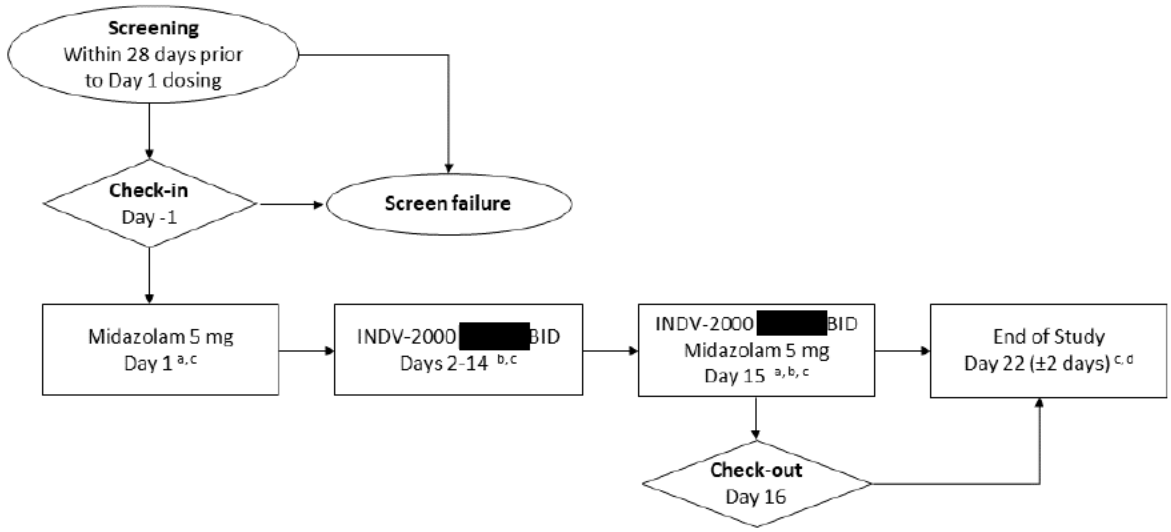
		Estimand		
Objective Clinical Category	**Statistical Category**	**Variable/Endpoint**	**Population**	**Population-Level Summary**
Safety	Exploratory	Observed values and changes from baseline (pre-dose Day 1) in sedation visual analogue scale (VAS) score through Day 15.	Safety	Numeric descriptive
		Observed values and changes from baseline (Day -1) through Day 22 in laboratory results	Safety	Numeric or categorical descriptive
		Observed values and changes from baseline (pre-dose Day 1) through Day 22 in electrocardiogram (ECG) results	Safety	Numeric or categorical descriptive
		Observed values and changes from baseline (pre-dose Day 1) through Day 22 in vital signs	Safety	Numeric descriptive
		Observed values and changes from baseline (Day -1) through Day 22 in physical examination	Safety	Categorical descriptive
		Observed values and changes from baseline (Day -1) through Day 22 in suicidal ideation and behavior [as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)]	Safety	Categorical descriptive

1.2. Study Design

This is a Phase I open-label, single-center, fixed-sequence study in healthy adults to evaluate the potential cytochrome P450 3A4 (CYP3A4) induction effect of INDV-2000 using oral midazolam as a probe.

The study schematic is depicted in Figure 1.

Figure 1. Study Schematic



Key features of the study design are described below.

- Approximately 20 healthy adults will be enrolled to yield at least 16 evaluable participants, defined as participants with plasma concentration-time profiles sufficient for calculation of PK parameters during the study.

[redacted]

- All participants who received at least one dose of study drug (including participants who terminated the study early) will return to the study site 7 ± 2 days after the last dose for EOS procedures and to determine if any AEs has occurred since the last study visit.

2. STATISTICAL HYPOTHESES

This study was not formally powered to test specific statistical hypotheses. Neither an estimate of within-subject variability nor no-effect boundaries for 90% CIs of geometric means were pre-specified.

2.1. Multiplicity Adjustment

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

3. SAMPLE SIZE DETERMINATION

A maximum of 20 participants will be assigned to receive the study drugs. This sample size is based on earlier clinical experience and is expected to provide at least 16 evaluable participants, defined as participants with plasma concentration-time profiles sufficient for calculation of PK parameters during the study.

4. POPULATIONS FOR ANALYSIS

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

Table 3 Analysis Populations

Population	Description
Screened	Participants who signed informed consent.
Safety Analysis Set	Participants who received at least one dose of study drug.
PK Analysis Set	Participants who received at least one dose of study drug, had an adequate number of PK samples collected to derive any PK parameter, and who had no protocol deviations that would have significantly altered plasma concentrations of study drugs.

5. STATISTICAL ANALYSES

5.1. General Considerations

5.1.1. Timing of Analyses

Safety data will be reviewed on an ongoing basis. There will be a production run of tables, figures, and listings (TFLs) after the database has been locked following the study-level EOS.

5.1.2. Programming Environment

SAS® version 9.4 or higher (SAS Institute, Cary, North Carolina) will be used for statistical analyses and for 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 summarized by visit for visit-based assessments and by treatment for non-visit-based assessments, if applicable. 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 for non-visit-based assessments, where applicable, will be Midazolam, INDV-2000 + Midazolam, INDV-2000, All Subjects; some of these tables may omit the All Subjects groups. Tables and figures for visit-based assessments will only show All Subjects and will include a footnote to describe treatments administered for each visit, if applicable.

- 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"), where applicable. Sample sizes reported as part of descriptive statistics ("n") will be the number of non-missing observations.

- Listings will generally include unique subject identifier; treatment, if applicable, if the assessment is not visit-based; 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 original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original 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 6.4.1 (Appendix 4) 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

Study Drug: INDV-2000 or midazolam

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

Day -1 Clinic Check-In: clinic check-in to date/time of dosing on Day 1.

Study Day 1: day of first dose of study drug.

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

Duration (unless otherwise specified):

- Duration in days = end date – start date + 1
- Duration in minutes = end time – start time

Baseline observation: for a given parameter for a given subject, the last observed value, including unscheduled and repeated assessments, before the first dose of study drug.

EOS, Subject-Level: Early termination or completion of last scheduled visit.

EOS, Study-Level: Last visit for last subject.

5.2. Study Conduct and Participant Disposition

Subject disposition summaries will include the number of subjects screened and the number and percentage of subjects who were screen failures, who were enrolled, who were in each analysis population, and who completed the study. For percentages, the number of subjects screened will be the denominator for screen failures and for subjects enrolled, and the number of subjects enrolled will be the denominator for the Safety Analysis Set, the PK Analysis Set and for subjects completing the study.

Reason for study discontinuation will also 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:

- Midazolam C_{max} following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15

- Midazolam $AUC_{0-\infty}$ following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15
- Midazolam AUC_{last} following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15
- 1-hydroxymidazolam C_{max} following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15
- 1-hydroxymidazolam $AUC_{0-\infty}$ following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15
- 1-hydroxymidazolam AUC_{last} following dosing of midazolam on Day 1 and dosing of midazolam + INDV-2000 on Day 15

5.3.2. Main Analytical Approach

Estimand strategy: Principal stratum.

Analysis set: PK (see Table 3).

Analysis methodology: Standard non-compartmental methods based on actual sampling times will be used to derive parameters for each subject on each of days 1 and 15 (see Appendix 6.4.1). A random effects model will be used to estimate the ratio of geometric means between absence and presence of INDV-2000, with a 90% CI. In this model, the log-transformed parameter value will be the dependent variable, day (1 or 15) will be the independent variable, and subject will be treated as a random effect.

For interpretation of AUC geometric mean point estimates, the guidance document Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry[1] provides the following classification information for an investigational drug:

- A strong inducer decreases the AUC of a sensitive index CYP substrate by ≥ 80 percent.
- A moderate inducer decreases the AUC of a sensitive index CYP substrate by ≥ 50 to < 80 percent.
- A weak inducer decreases the AUC of a sensitive index CYP substrate by ≥ 20 to < 50 percent.

In other words, in terms of clinical significance, an investigational drug may be classified as a strong, moderate, or weak inducer of a sensitive CYP substrate based on an estimate of the AUC geometric mean ratio as follows:

Classification	If the point estimate of the AUC geometric mean ratio
Strong inducer	≤ 0.2
Moderate inducer	> 0.2 and ≤ 0.5
Weak inducer	> 0.5 and ≤ 0.8

Intercurrent events and missing data: Subjects with intercurrent events may be excluded from the PK Analysis Set, 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.

5.4. Secondary Endpoints Analysis

5.4.1. Definition of Endpoints

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

5.4.2. 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 6.6.2 (Appendix 6) for handling of missing AE information.

See Section 5.5.2 for details on AE summaries and listings.

5.5. Exploratory Endpoints Analysis

5.6. Other Safety Analyses

5.6.1. Study Drug Exposure

Study drug exposure will be summarized for the Safety Analysis Set as total dose and dose duration (days), separately for midazolam and INDV-2000. Dose duration will be defined as number of days at least 1 dose was taken.

5.6.2. Adverse Events

A TEAE starts at or after the first dose of study drug. 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 study drug; 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 study drug discontinuation or interruption, and fatal TEAEs will be listed separately.

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

TEAEs, TESAEs, study drug-related TEAEs and TESAEs will be summarized by MedDRA SOC and PT, each in descending order of frequency among all subjects (then alphabetically in case of ties). TEAEs will also be summarized by maximum severity and by maximum toxicity 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 tables.

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

Non-TEAEs are defined as AEs that started before first dose of study drug. Non-TEAEs will be summarized for the Safety Analysis Set.

See Section 6.6.2 (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 4) 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, $<$, $\leq$, $>$, $\geq$) will be listed as reported but will be summarized without the qualifier.

Table 4 Planned Laboratory Evaluations

Haematology

- Haemoglobin
- Haematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation

- Prothrombin time/INR
- Activated partial thromboplastin

Serum Chemistry *

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase (ALP)
- AST
- ALT
- Gamma-glutamyl Transferase
- Albumin
- Sodium
- Potassium
- Chloride
- Glucose (fasting)
- Creatinine **
- Total protein
- Total cholesterol
- Triglycerides
- Creatine phosphokinase

Urinalysis

- pH
- Specific gravity
- Protein ***
- Glucose
- Ketones
- Bilirubin
- Blood ***
- Nitrite***
- Urobilinogen
- Leukocyte esterase ***

Additional Tests

- HIV-1; HIV-2 (screening only)
- HBsAg (screening only)
- HCV antibodies (screening only)
- Urine drug screen
  - Opiates §
  - Opioids
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
  - Fentanyl
  - Oxycodone
- Urine alcohol screen
- Serum pregnancy test (for females only; screening only)
- Urine pregnancy test (for females only)
- FSH (for PMP females only; screening only)
- COVID-19 PCR (check-in only)

* Serum chemistry tests will be performed after at least an 12-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 12 hours prior to when the serum chemistry sample is taken.

** At the Screening Visit, creatinine clearance will be calculated using the Cockcroft-Gault formula.

*** If urinalysis is abnormal for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

5.6.3.2. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, pulse oximetry) will be summarized as observed values and changes from baseline by analysis visit and time point.

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. ECG interpretation (normal, abnormal not clinically significant, abnormal clinically significant) will be summarized by visit and time point as shifts from baseline.

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 Behaviour
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.

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 analysis sets, if different. Parameters to be summarized will include age, sex, race, ethnicity, fertility status, and height/weight/body mass index.

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 analysis set.

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 ended before first administration of study drug or were taken by subjects who never took study drug. All other medications and therapies will be considered concomitant.

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

See Section 6.6.3 (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, important, not important), per the Protocol Deviation Assessment Tool for the study, for the safety analysis set. Deviations that occur in subjects who were not in the safety analysis set, 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
ADaM	Analysis Data Model
AE	adverse event
ATC	Anatomic Therapeutic Chemical
AUC	area under the curve
AUC_{0-12h}	area under the curve from 0 to 12 hours post dose
$AUC_{0-\infty}$	area under the curve from 0 to infinity
AUC_{last}	area under the curve from dosing to the last measured concentration
BLQ	below limit of quantification
C-SSRS	Columbia-Suicide Severity Rating Scale
CI	confidence interval
C_{max}	maximum plasma concentration
CRF	Case Report Form
CSR	Clinical Study Report
C_{trough}	Trough concentration
CV	coefficient of variation
CYP	cytochrome P450
CYP3A4	cytochrome P450 3A4
ECG	electrocardiogram
EOS	end of study
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetic
PT	Preferred Term
QTcF	Fridericia's corrected QT interval
SAP	Statistical Analysis Plan
SD	standard deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
$t_{1/2}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFLs	tables, figures, and listings
T_{max}	time of maximum plasma concentration
VAS	visual analogue scale
WHO-DD	World Health Organization Drug Dictionary

6.2. Appendix 2: Changes to Protocol-Planned Analyses

None.

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 Case Report Form (CRF). An early termination visit will be counted as a scheduled visit if it occurs on a scheduled visit study day; otherwise, it will be counted as an unscheduled visit. 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

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 or higher, Certara, LP).

6.5.1.1. Concentration

6.5.1.2. Plasma PK Parameters

6.6. Appendix 6: Methods to Manage Missing Data

6.6.1. BLQ PK Concentrations

6.6.2. 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 Study Drug

Missing relationship to study drug 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 serious adverse event 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 Analysis Set, 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 study drug administration.

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

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

- Missing start time if start date is on or after first date of study drug administration.

6.6.3. Medications and Therapies

Missing Start and End Date/Time Information for Medications and Therapies

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

Non-missing end year and month, missing end day

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

Non-missing end year, missing end month and day

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

1. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, January 2020.