Statistical Analysis Plan

Protocol No. SCY-078-121, Version 4 (Amendment 3), 13 March 2024

An Open-Label Pharmacokinetic Study in Healthy Lactating Women after Two Oral Doses of Ibrexafungerp Administered on a Single Day

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Signature Page

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Version History

Version Number	Version Date	Author	Significant Changes from Previous Versions
1.0	25 March 2024	Ramesh Vishwakarma	(not applicable)

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
AM	Ante meridiem
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-t}	Area under the concentration-time curve from 0 to t hours
ATC	Anatomical therapeutic class
BID	Twice a day
BMI	Body mass index
BP	Blood pressure
BLQ	Below the limit of quantification of the assay
C_{av}	Average concentration in breast milk during the dosing interval
CI	Confidence interval(s)
CL/F	Clearance
C_{max}	Maximum concentration
C_{min}	Minimum concentration
CS	Clinically significant
CSP	Clinical study protocol
CV	Coefficient of variation
DBL	Database lock
ECG	Electrocardiogram
ECI	Event of clinical interest
EMA	European Medicines Agency
eCRF	Electronic case report form
FDA	Food and drug administration
GSD	Geometric standard deviation
GCV	Geometric coefficient of variation
HR	Heart rate
ICH	International conference on harmonization
MedDRA	Medical dictionary for regulatory activities
M/P	Milk/Plasma
µg	Microgram
µL	Microliter
mg	Milligram
mL	Milliliter

ng	Nanograms
nM	Nanomolar
NR	Not reportable
NS	No sample
NCA	Noncompartmental analysis
OTC	Over-the-counter
PK	Pharmacokinetics
PM	Post meridiem
PT	Preferred term
Q12H	Every 12 hours
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
T	Temperature
TLF	Tables, figures, and listings
$t_{½}$	Terminal half-life
TEAE	Treatment emergent adverse event
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
WBC	White blood cell
V_d	Volume of distribution
VVC	Vulvovaginal candidiasis

1 Introduction

The Statistical Analysis Plan (SAP) provides details of the planned analysis and reporting for Scynexis Inc. Protocol SCY-078-121 (An Open-Label Pharmacokinetic Study in Healthy Lactating Women after Two Oral Doses of Ibrexafungerp Administered on a Single Day), final version 4.0 (Amendment 3) dated 13-March-2024.

The structure and content of this SAP provide sufficient details to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) for statistical practice.

The planned statistical methodology to be used in this SAP describes the main variables and populations, anticipated data transformation and manipulation methods, and other details of the analyses (for producing Tables, Figures, and Listings (TLFs)) not provided in the Clinical Study Protocol (CSP).

The following documents were reviewed in preparation of this SAP:

- Study Protocol, Version 4.0 (Amendment 3) (13 MAR 2024)
- electronic Case Report Form (eCRF), Version 1.3 (18 OCT 2023)

The SAP will be finalized prior to database lock (DBL) and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if improved methods of analysis should arise, updates to the analyses may be made. Any deviations from the SAP after DBL, reasons for such deviations, and all alternative or additional statistical analyses that may be performed will be described in an SAP Addendum and documented in the final clinical study report.

2 Study Objectives

2.1 Primary Objectives

- To determine whether ibrexafungerp is excreted in breast milk and if so, to characterize ibrexafungerp pharmacokinetics (PK) in the breast milk and plasma of lactating women.

2.2 Secondary Objectives

- To calculate the potential infant exposure to ibrexafungerp if lactating women are treated with ibrexafungerp.
- To characterize the safety and tolerability of ibrexafungerp in lactating women.

3 Study Endpoints

3.1 Primary Endpoints

- The plasma pharmacokinetic parameters: area under the curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), plasma clearance or apparent oral clearance (CL/F), apparent volume of distribution (V_d), and terminal half-life ($t_{1/2}$).
- The breast milk pharmacokinetic parameters: area under the curve (AUC) for the

different collection periods, average concentration (C_{av}), C_{max}, C_{min}, and T_{max}.

3.2 Secondary Endpoints

- Calculated Daily Infant Dosage (mg/day) after maternal ingestion for one day of 300 mg BID ibrexafungerp dosing.
- Calculated Relative Infant Dose (%) after maternal ingestion for one day of 300 mg BID ibrexafungerp dosing.
- Safety and tolerability as measured by adverse events, vital signs, physical examination, and clinical laboratory assessments.

4 Study Design and Methods

4.1 Overall Study Design

This is a Phase 1 study designed to determine whether the given oral dose of ibrexafungerp is excreted in breast milk, and if so, to characterize ibrexafungerp PK in the breast milk and plasma of lactating women.

Participants will receive a single day of twice daily (BID) 300-mg (2 x 150-mg) oral ibrexafungerp doses given 12 hours apart (Q12H). Participants will receive both doses on site. Participants will be admitted to the clinic on Day 1, and may be discharged on Day 5, after the 108-hour procedures are completed, at the discretion of the Investigator.

Participants who discontinued may be replaced at the discretion of the investigator and Sponsor to ensure that up to 10 evaluable participants complete the study. The flow chart of the study design is given in Figure 1 and the Schedule of Assessments is provided in Table 1.

*Figure 1:: **Study Design***

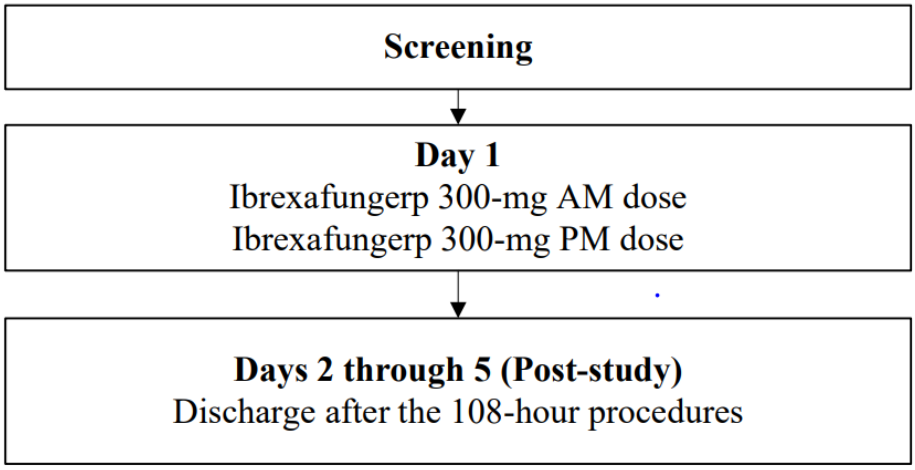

Table 1 **: *Schedule of Assessments***

Study Procedures	**Screening[a]**	**Day 1**					**Day 2**	**Day 3**	**Day 4**	**Day 5 Post-study**
		Predose[b]	**0 hr**	**8 hr**	**12 hr**	**24 hr**	**36 hr**	**48 hr**	**72 hr**	**108 hr**
Informed Consent	X									
Inclusion/Exclusion	X	X								
Physical Exam[c]	X	X								X
12-Lead ECG[c]	X									
Enrollment		X								
Demographics and Medical History prior 1 yr (including pregnancy, postpartum, and lactation history)	X									
Height and Weight[d]	X									X
Vital Signs (HR, BP)[c]	X	X		X		X				X
Vital Signs (RR, Temperature)	X	X								X
Safety laboratory testing[e]	X	X								X
HIV/Hepatitis Screen	X									
COVID, Alcohol, and Urine drug screen (standard at site)[f]	X	X								
Pregnancy Tests (serum)	X	X[j]								X
Standard Meals		X----------								----X
Study Drug Administration[g]			X		X					
Blood Samples for Ibrexafungerp Concentration[h]			X----------							----X
Breast Milk Samples for Ibrexafungerp Concentration[i]			X----------							----X

Abbreviations: BP = blood pressure; HR = heart rate; RR = respiratory rate, PK = pharmacokinetic, ECG = electrocardiogram, and HIV = human immunodeficiency virus

[a] Pre-study screening to determine eligibility may be performed within 4 weeks prior to dosing with study medication.

[b] The Day 1 predose examinations and assessments may be performed up to 12 hours predose.
[c] During physical examination at screening and predose participants will also be asked about physical activity. Prior to ECG the participants must be in a semi-recumbent position for at least 10 minutes prior to having heart rate, blood pressure, and ECG performed.
[d] Height documented at screening only.
[e] Participants will not be required to fast prior to collecting blood and urine for laboratory safety tests. At screening a full set of laboratory tests (hematology, coagulation, chemistry, and urinalysis) will be assessed; at pre-dose only hematology, AST, ALT, and bilirubin will be assessed; and at poststudy only hematology and clinical chemistry will be assessed (coagulation will not be required).
[f] Urine drug and alcohol screening will be done at screening, within 12 hours before the first dose, and upon admission to the clinic. COVID-19 testing will be done per site requirements.
[g] Ibrexafungerp 300-mg will be administered BID Q12H on Day 1 while the participant is in a semi-supine position with 240 mL of room temperature water.
[h] Plasma samples will be obtained at the following timepoints: 0 hours (prior to first dose), and at 2, 6, 8, 12, 24, 36, 48, 72 and 108 hours post first dose of study drug for determination of ibrexafungerp in plasma concentrations. The 12-hour samples will be taken prior to the second dose of ibrexafungerp.
[i] Breast Milk: **complete expression** of milk from both breasts (using a standard electric breast pump) will be obtained at the following timepoint and intervals: pre-dose, 0-2, 2-4, 4-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, and 72-108 hours post first dose of study drug.
[j] Pregnancy test to be repeated if screening was more than 24 hours prior to Day 1 dosing.
[k] Admission to the clinic will be prior to dosing on Day 1 (for participant, and infant if that is the participant's choice). Infant admission is not mandatory, but the site will provide this option. The stay in the clinic will be through the Day 5, 108-hour, post-study procedures are complete.

4.2 Sample Size

There is no formal power calculation. The sample size (N) is based on practical aspects of recruitment in this population. A sample size of up to 10 participants to complete the study is selected.

Up to t10 healthy lactating females who are at least 10 days postpartum with a full milk supply established and are between the ages of 18 and 50 years, inclusive, at the time of screening. Enough participants will be enrolled to complete up to 10 evaluable participants (meeting study inclusion/exclusion criteria specified in the protocol).

4.3 Treatment of Participants

The Sponsor will provide the study site with adequate clinical supplies including: 150-mg ibrexafungerp tablets of the citrate salt formulation. Participants will be assigned the investigational product (See Table 2). Please refer to the protocol on prior and concomitant medications use and the study restrictions.

*Table 2 : **Investigational Product***

	Investigational Product
Product Name:	Ibrexafungerp tablets (as citrate salt)
Dosage Form:	150-mg ibrexafungerp tablets (as citrate salt)
Unit Dose:	2 X 150-mg tablets for the 300-mg dose
Route of Administration:	Oral
Physical Description:	150-mg compressed tablets
Manufacturer:	SCYNEXIS, Inc.

4.4 Randomization and Blinding

There is no randomization planned in the study. This is an open-label study. Each participant will be assigned a participant's study number (in numerical order as they are enrolled) prior to dosing. The participant's study number will be used to identify the participant for all procedures and in eCRF.

4.5 Study Measurements

Study measurements are taken (see Table 1) on measurements collected by timepoint:

- Prestudy Screening (Day -28 to Day -1)
- Predose (Prior to Day 1 Morning Dosing)
- Treatment Day 1
- Day 2 (24-hours postdose) through Day 4
- Day 5 (Post-Study)

4.5.1 Pharmacokinetic Measurements

For pharmacokinetic (PK) assessments, the concentration of ibrexafungerp will be obtained from the blood sample and breast milk sample.

The blood samples will be obtained at the following timepoints: 0 hours (prior to first dose), and at 2, 6, 8, 12 (prior to second dose), 24, 36, 48, 72 and 108 hours post first dose of study drug for determination of ibrexafungerp concentrations in plasma. The 12-hour samples will be taken prior to the second dose of ibrexafungerp.

In breast milk, complete expression of milk from both breasts (using a standard electric breast pump) will be obtained at the following timepoint and intervals: pre-dose, 0-2, 2-4, 4-8, 8-12, 12-18, 18-24, 24-36, 36-48, 48-72, and 72-108 hours post first dose of study drug.

4.5.2 Safety Measurements

The safety and tolerability of ibrexafungerp will be monitored by clinical assessment of adverse experiences and by repeated clinical and laboratory measurements, including vital signs (heart rate, blood pressure, respiratory rate, and temperature), physical examinations, 12 lead electrocardiograms (ECGs), standard laboratory safety tests (hematology, coagulation, chemistry, and urinalysis).

4.6 Data Handling

All participant data used for analysis will be displayed in listings.

Summaries for continuous variables will include the descriptive statistics for number of participants (n), mean, standard deviation (SD), minimum (min), median, and maximum (max). For PK concentration and parameters, the summary table will also include statistics: percent coefficient of variation (CV%), geometric mean (GM), SD of GM (GSD) andpercent CV of GM (GCV%). Summaries for categorical (discrete) variables will include the number and/or percentage of participants in a particular category. When categorical data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non- zero counts. The denominator for all percentages, unless otherwise specified, will be the number of participants in the specified analysis population.

For presentation of numeric data, minimum and maximum values will be presented to the same number of decimal places as the electronic Case Report Form (eCRF) data; means and medians will be presented to one more decimal place than the eCRF data; standard deviations will be presented to two more decimal places than the eCRF data.

Baseline is defined as the last non-missing value measured prior to the first dose of study drug. Change from Baseline is defined as [Post-baseline Value – Baseline Value]. Statistical analyses and summaries will be performed using SAS® Version 9.3 or greater (SAS Institute). Pharmacokinetic analyses will be performed using Phoenix WinNonlin Version 8.4 (Certara USA, Inc.).

5 Data Analysis

5.1 Analysis Populations

The following analysis population will be used to summarize the results from this study:

- **Enrolled Population**: All participants who were signed informed consent

and met the study eligibility criteria.

- **Safety Population**: All participants who were enrolled in the study and received at least a partial tablet of ibrexafungerp. No treated participants will be excluded from the safety population.
- **Pharmacokinetic Population**: All participants who receive ibrexafungerp and who have at least one quantifiable PK parameter.

Participants who are excluded from the analysis populations will be listed by participant and treatment.

5.2 Study Participants

5.2.1 Participant Disposition

The number and percentage of participants belongs to each analysis population as defined in Section 5.1 will be summarized and listed for all enrolled participants.

Participant disposition will be summarized using the number of participants who were enrolled, the number and percent of participants who complete the study, the number and percent of participants who discontinue the study, and the reasons for discontinuation. The denominator of percentage will be the number of participants enrolled. Participant disposition and completion status will be listed for all enrolled participants.

5.2.2 Protocol Deviations

Protocol deviations will be determined with complying with all IRB-established procedures. Protocol deviations will be listed by participant and treatment for all enrolled participants.

5.2.3 Participant Eligibility

Eligibility status based upon meeting protocol entrance criteria will be listed for all enrolled participants.

5.3 Participant Demographics

Demographics will be summarized using the safety population. The demographics consist of age, gender, race, ethnicity, height, body weight, and body mass index [BMI]. Individual demographics for the safety population will be listed by participant.

5.4 Medical History

During screening, a complete medical history for the prior 1 year will be recorded for each participant. Medical history will include medical diagnoses, major surgical procedures, pregnancy, postpartum, and lactation history.

Medical condition and/or significant medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.1 or later and listed by reported term, System Organ Class (SOC), and Preferred Term (PT). The number and percentage of participants will be summarized by SOC and PT for Safety Population.

Medical/surgical history will be listed by participant in the safety population. Listing will be sorted by descending total of ATC level and alphabetically in lower level.

5.5 Prior and Concomitant Medications

All medications (including prescription and OTC medications) taken within 14 days before dosing (Day 1) with study medication throughout the study, and through poststudy visit will be coded using WHO Drug Enhanced Dictionary (September 2023 version B3). Prior Medication and Concomitant Medication are defined as below:

- Prior medications are defined as medications that stop prior to the first dose of study drug.
- Concomitant medications are defined as medications that start within the period starting from the beginning of the screening period to the end of study (Day 5), and with end date no earlier than the first dose of study drug.

Medications with missing or partially missing start or end dates will be handled per the conventions described in Appendix B. If it cannot be determined whether a medication was a prior medication due to missing or partial medication start or end dates, the medication will be considered concomitant. Concomitant medications will be summarized by Anatomical Therapeutic Class (ATC) level 1, ATC level 2, and Preferred Term. Prior and concomitant medications will be listed for each participant by treatment, Preferred Term, reported term, ATC level 1, ATC level 2, including the start and end dates, prior/concomitant flag, whether it is ongoing, dose, unit, frequency, route of administration and indication. The prohibited concomitant medications will be listed and tabulated in the same way as concomitant medications. Listing will be sorted by descending total of ATC level and alphabetically in lower level.

5.6 Treatment Exposure and Compliance

The details of Ibrexafungerp treatment exposure and compliance, including actual dose (2 tablets x 150 mg or other), date time of dose, whether first treatment administered (yes/no), whether second treatment administered (yes/no) and reason for adjusted or missed dose will be listed by participant in the safety population. Percentage of compliance, number and percentage of participants with missing treatment or adjusted treatment will be summarized. The compliance will be calculated as total actual drug administered (mg) / total planned drug to be administered (mg) *100.

5.7 Pharmacokinetic Analysis

5.7.1 Plasma and Breast milk Concentrations

In displays of plasma and breast milk concentration summary statistics (and in PK analyses), all plasma concentrations below the limit of quantification (BLQ) of the assay will be treated as “0” if they occur before the first measurable or after the last measurable concentration, and will be set as missing for data points in between two measurable concentrations. If a sample is missing or the value is not reportable and is between two measurable concentrations, the value at that time point will be left blank for the analysis and reported as either Not Reportable (NR) or No Sample (NS).

Individual participant plasma and breast milk ibrexafungerp concentrations, actual breast

milk and blood sampling dates and times, actual volume of breast milk collected at each time interval, actual dosing information (actual time and date of dosing, and actual dose taken) will be presented by participant in data listings.

Ibrexafungerp concentrations in plasma and in breast milk measured over time will be displayed graphically for individual participants and for all participants in the PK population and will be summarized descriptively based on nominal times. Linear and semi-log plots of geometric mean (SD) and individual ibrexafungerp concentration versus time profiles will be displayed. These linear and semi log plots will be generated separately for time restricting up to 24 hrs and for complete study duration (0-108 hrs). For geometric mean concentration-time profile plots, the nominal PK sampling time will be used, for individual concentration-time profile plots, the actual PK sampling time will be used.

The daily infant dosage (total drug present in milk and consumed by the infant per day) will be calculated as follows:

- Calculated Daily Infant Dosage (mg/day) = Σ (total drug concentration in each milk collection multiplied by the expressed milk volume in each milk collection)

The Milk Plasma Ratio (M/P) will be calculated. M/P = AUC_{0-24} milk/AUC_{0-24} plasma.

The calculation of Milk plasma ratio (M/P) should be based on AUC and on multiple time points over 24 hours and not just a single point in time.

Milk plasma ratio (M/P) = AUC_{0-24} milk /AUC_{0-24} plasma

The relative infant dose (the percent of the weight-adjusted maternal dosage consumed in breast milk over 24 hours) will be calculated:

- Calculated Relative Infant Dose = Infant Dosage (mg/kg/day)/Maternal Dosage (mg/kg/day) multiplied by 100

A table will be provided to include summary statistics on daily infant dosage, relative infant dose, and M/P based on AUC_{0-24}. A listing of infant dose will be provided by time-point.

5.7.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived for ibrexafungerp in plasma and in breast milk for participants in the PK population. Pharmacokinetic parameters are defined in Table 3.

*Table 3 : **Pharmacokinetic Parameters***

Parameter	Description
C_{max}	Maximum concentration in plasma/breast milk
C_{min}	Minimum concentration in breast milk
C_{av}	Average concentration in breast milk during the dosing

	interval
AUC_{0-24}	Area under the plasma/breast milk concentration-time curve from time zero to 24 hours
M/P	AUC_{0-24} milk /AUC_{0-24} plasma
T_{max}	Time to reach maximum plasma/breast milk concentration
AUC_{0-t}	Area under the plasma/breast milk concentration from time zero to t_{last}
AUC_{0-inf}	Area under the plasma/breast milk concentration from time zero extrapolated to infinity
AUC%extrapolated	Percentage of AUC_{0-inf} due to extrapolation from t_{last} to infinity.
K_{el} or λ_z	Elimination rate constant in plasma
$t_{½}$	Elimination half-life in plasma
CL/F	Clearance or apparent oral clearance in plasma
V_d	Apparent volume of distribution in plasma

PK parameters will be presented by participant in data listings and will be summarized by participants in the PK population using descriptive statistics.

The PK parameters of ibrexafungerp will include maximum concentration (C_{max}) following first dose, area under the concentration-time curve (AUC_{0-24}) time to maximum concentration (T_{max}) after the first dose, and elimination half-life ($t_{½}$) after the second dose that will be calculated by means of noncompartmental analysis (NCA) using Phoenix WinNonlin Version 8.4 (Certara USA, Inc.). AUC_{0-24} in milk to plasma ratio is of primary interest to the study objectives. In addition, since blood samples and breast milk will be collected to 108 hours, AUC_{0-t} and AUC_{0-inf} will also be calculated and presented.

Elimination rate constants and AUC determination will be based on the linear trapezoidal rule, and actual PK sample times will be used for the PK analyses. The t½, if calculated, will use at least 3 time points from the logarithmic terminal phase portion of the concentration time curve. Pharmacokinetic parameters derived with Kel such as t½ and AUC_{0-inf}, will be listed but excluded from descriptive statistics if R^2_adjusted < 0.8 in λz (Kel) estimation.

For determination of AUC_{0-inf}, if the percentage of extrapolated AUC is more than 20% of AUC_{0-inf} from t_{last} to infinity, then individual AUC_{0-inf} result will be listed but flagged as not reliable calculation. AUC_{0-inf} for these flagged subjects will not be included in descriptive statistics table.

The following plasma ibrexafungerp pharmacokinetic parameters will be calculated: area under the curve (AUC), peak plasma concentration (C_{max}), time to peak plasma concentration (T_{max}), plasma clearance or apparent oral clearance (CL/F), apparent volume of distribution (V_d), and terminal half-life ($t_{1/2}$).

The following PK parameters of ibrexafungerp in breast milk will be calculated: AUC

for the different collection periods, C_{av} based on AUC derived from collections at different time points above; total milk concentration data will be used to calculate C_{max}, C_{min} and T_{max}. The C_{av} is calculated as follows.

$C_{av} = AUC_{0\text{-}24} / 24 \cdot h$

Plasma and breast milk PK parameters for individuals will be listed and summarized descriptively.

Plasma and breast milk concentrations and PK parameters will be summarized using descriptive statistics. Summary statistics for PK parameters except for T_{max} will be described by n, arithmetic mean (mean), arithmetic mean SD, arithmetic CV%, geometric mean, geometric SD, geometric CV%, min, median and max. For T_{max}, summary statistics will be described by n, median, min and max. For t½, harmonic mean and pseudo SD will also be presented. CV% will be displayed in one decimal place.

5.8 Safety Analysis

The safety and tolerability of ibrexafungerp will be assessed by the evaluation of adverse events, vital signs (blood pressure, heart rate, respiratory rate, and temperature), physical examination, 12-lead electrocardiogram (ECG), and laboratory safety (biochemistry, hematology, coagulation and urinalysis).

Safety variables will be listed by all participants in the Safety Population.

5.8.1 Adverse Events

Adverse events (AEs) will be collected from the time of informed consent throughout the study, up through the poststudy visit.

All AEs will be coded and classified according to MedDRA (Version 26.1 or later). The intensity of adverse events is judged by the Investigator as mild, moderate or severe; a causal relationship to study drug is judged by the Investigator as probably related, possibly related or unrelated; outcome of an adverse event is judged by the Investigator as recovered/resolved and not recovered/not resolved. Treatment-emergent adverse events (TEAEs) are defined as 1) AEs with an onset date and time after the first dose of study drug, or 2) any event already present that worsens in severity after exposure to the treatment.

A serious adverse event (SAE) is an AE occurring during any study phase (ie, baseline, treatment, or follow-up), and at any dose of the investigational product that fulfils one or more of the following: 1) Results in death; 2) It is immediately life-threatening; 3) It requires in-participant hospitalization or prolongation of existing hospitalization; 4) It results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions; 5) Results in a congenital abnormality or birth defect; 6) It is an important medical event that may jeopardize the participant or may require medical intervention to prevent one of the outcomes listed above. The following are considered events of clinical interest (ECIs):

- Overdose

- Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) > 3 x ULN, confirmed by repeat laboratory test
- Hypersensitivity Reactions

Significant adverse events of particular clinical importance, other than SAEs and those AEs leading to discontinuation of the participant from the study, will be classified as other adverse events (OAEs). For each OAE, a narrative may be written and included in the Clinical Study Report.

A summary table of AEs will be created containing: number of AEs, number of TEAEs, number of participants with TEAEs, number of participants with treatment-related TEAEs, number of serious TEAEs, number of participants with serious TEAE, number of participants with treatment-related serious TEAEs, number of serious AEs, number of participants with serious AEs, number of events of clinical interest (ECIs) and AEs leading to death, AEs leading to study discontinuation, AEs leading to treatment interruption, AEs leading to treatment discontinuation.

All TEAEs will be summarized as the number and percentage of participants by SOC, PT. Missing or partially missing start and end dates for AEs will be handled according to the conventions detailed in Appendix A. For cases where ascertaining treatment-emergence is unlikely, the event will be categorized as treatment-emergent AE. Separate summaries will be created by severity and by relationship to study drug. If the same AE (PT) is reported more than once for the same participant, it will only be counted once in the summary table. For summary tables by severity and relationship to study drug, if the same AE (PT) is reported more than once for the same participant, the highest severity grade (severe > moderate > mild) or the strongest relationship to treatment (probably related > possibly related > unrelated) will be counted in the summary table. All SAEs, AEs leading to study discontinuation and AEs leading to death will be summarized by SOC and PT.

All AEs will be listed, and a flag will indicate if the AE is treatment emergent and a flag will indicate if the AE is unexpected adverse event.

All serious AEs (SAEs) will be listed, and a flag will indicate if the SAE is treatment emergent.

All adverse events leading to study discontinuation will be listed by participant.

All adverse events leading to death will be listed by participant. All ECI will be listed by participant.

5.8.2 Clinical Laboratory Assessments

Hematology, coagulation, blood chemistry, urinalysis, alcohol, and urine drug screens, pregnancy screen, serology, and COVID-19 test will be performed as described in the schedule of assessment Table 1.

Descriptive statistics for baseline value, actual value will be provided for clinical hematology, coagulation, chemistry laboratory tests and quantitative urinalysis including pH. The change from baseline value to Day 5 post study will be provided for hematology

and clinical chemistry. Baseline for clinical laboratory tests is defined as the last non-missing assessment prior to administration of study drug. Conventional Units will be used for reporting the laboratory test results. Unscheduled lab visit assessments will be excluded from summary tables but will be provided in the listings.

Values for any chemistry, hematology, coagulation and urinalysis values outside the clinical reference ranges, clinically significant or not will be flagged on the individual participant data listings. Laboratory test results will be assigned a low/normal/high (L/N/H) classification according to whether the value is below (low, L), within (normal, N), or above (high, H) the laboratory parameter's reference range. Shifts from baseline (L/N/H) to Day 5 post study (L/N/H) will be presented for hematology and clinical chemistry only.

Plots will be generated for laboratory parameters, including the absolute values and change from baseline values for hematology and clinical chemistry.

Alcohol and urine drug screens, serology, COVID-19 test, pregnancy screen results will be listed by participant.

5.8.3 Vital Signs Assessments

Vital signs, including blood pressure (BP systolic and diastolic), heart rate, respiratory rate, and body temperature will be measured at the timepoints indicated in Table 1.

All vital sign data including unscheduled records will be listed. Unscheduled records will be excluded from the summary statistics. Vital sign data including baseline value, actual value, and change from baseline to each post-baseline visit will be summarized by visit and timepoint. Abnormal or clinically significant (CS) vital signs will be flagged in the listings.

5.8.4 Physical Examinations

A standard physical examination will be performed at the timepoints indicated in Table 1.

Physical examination results will be listed by participant in the safety population.

5.8.5 Electrocardiogram (ECG)

A safety 12-lead ECG will be obtained and evaluated by a physician for the presence of abnormalities at screening indicated in the Schedule of Assessments in Table 1.

Participants should be resting in a semi-recumbent position for at least 10 minutes prior to having ECG readings obtained. ECG measurements will be single measurements.

Electrocardiogram examination will be listed for each ECG parameter in the safety population, including datetime collection, testing result, abnormal or not, clinically significant or not, specification if clinically significant.

5.9 Interim Analysis

An interim analysis will be conducted after five subjects have completed their

participation in the study. The analysis will involve the examination of pharmacokinetic and safety data and will comprise a full analysis as described in the SAP. The objective of the interim analysis is to determine whether the data from 5 participants is sufficient to address the objectives of the study and fulfill the post marketing requirement (PMR 4069-2); if not the study shall continue to recruit up to 10 participants.

The reporting analysis will involve descriptive statistical methods, including summaries, tabulations, graphs, or by-subject listings. Before initiating this analysis, the data for the study endpoints will undergo a thorough cleaning process, and the database will be soft-locked.

5.10 Statistical Programming and Deliverables

All statistical analyses, tables and listings will be generated in SAS (version 9.3 or later) with appropriate documentation and programming validation. The table of contents of all tables, figures, and listings will be presented in a TFLs shell supplemental document.

5.11 Changes to the Planned Analysis

Any deviation(s) of consequence from the SAP during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document, as appropriate.

APPENDIX A. ADVERSE EVENTS DATE IMPUTATION

AE Start Date	AE Stop Date	Algorithms
Known	Known	NA
	Partial	Impute stop date as the latest date possible (i.e., last day of month if day is missing or Dec 31 if day and month are missing). If the imputed stop date is later than the earlier date of data cutoff date and date of end of study, then use cutoff date or date of end of study, whichever is earlier, as the imputed AE stop date.
	Missing	Impute stop date as follows: (1) if study is ongoing: data cutoff date (2) if study discontinued: date of end of study
Partial	Known	Impute start date as follows: 1. If day missing only: (1) if same year-month as that of the start date of study drug: first dose date of study drug or AE end date, whichever is earlier (2) if different year-month from that of the start date of study drug: first day of month 2. If both month and day are missing: (1) if same year as that of the start date of study drug: first dose date of study drug or AE end date, whichever is earlier (2) if different year from that of the start date of study drug: January 1st of the year
	Partial	Impute start date as follows: 1. If day missing only: (1) if same year-month as that of the start date of study drug: first dose date of study drug (2) if different year-month from that of the start date of study drug: first day of month 2. If both month and day are missing: (1) if same year as that of the start date of study drug: first dose date of study drug (2) if different year from that of the start date of study drug: January 1st of the year Impute stop date as the latest date possible (i.e., last day of month if day is missing or Dec 31 if day and month are missing). If the imputed stop date is later than the earlier date of data cutoff date and date of end of study, then use cutoff date or date of end of study, whichever is earlier, as the imputed AE stop date.
	Missing	Impute start date as follows: 1. If day missing only: (1) if same year-month as that of the start date of study drug: first dose date of study drug (2) if different year-month from that of the start date of study drug: first day of month

		2. If both month and day are missing: (1) if same year as that of the start date of study drug: first dose date of study drug (2) if different year from that of the start date of study drug: January 1st of the year Impute stop date as follows: (1) if study is ongoing: data cutoff date (2) if study discontinued: date of end of study
Missing	Known	Impute start date as the first dose date of the study drug or AE end date, whichever is earlier.
	Partial	Impute start date as the first dose date of the study drug. Impute stop date as the latest date possible (i.e., last day of month if day is missing or Dec 31 if day and month are missing). If the imputed stop date is later than the earlier date of data cutoff date and date of end of study, then use cutoff date or date of end of study, whichever is earlier, as the imputed AE stop date.
	Missing	Impute start date as the first dose date of the study drug. Impute stop date as follows: (1) if study is ongoing: data cutoff date (2) if study discontinued: date of end of study

APPENDIX B. CONCOMITANT MEDICATIONS DATE IMPUTATION

CM Start Date	CM Stop Date	Algorithms
Known	Known	If stop date < start date of study drug: PRIOR If stop date ≥ start date of study drug, and start date ≤ end of study: CONCOMITANT If stop date ≥ start date of study drug and start date > end of study: POSTTREATMENT
	Partial	Impute stop date as the latest date possible (i.e., last day of month if day missing or Dec 31 if day and month are missing), then: If stop date < start date of study drug: PRIOR If stop date ≥ start date of study drug, and start date ≤ end of study: CONCOMITANT If stop date ≥ start date of study drug, and start date > end of study: POSTTREATMENT
	Missing	No PRIOR assignment if stop date is missing If start date ≤ end of study: CONCOMITANT If start date > end of study: POSTTREATMENT
Partial	Known	Impute start date as the earliest date possible (i.e., first day of month if day missing or Jan 01 if day and month are missing), then: If stop date < start date of study drug: PRIOR If stop date ≥ start date of study drug and start date ≤ end of study: CONCOMITANT If stop date ≥ start date of study drug and start date > end of study: POSTTREATMENT
	Partial	Impute start date as the earliest date possible (i.e., first day of month if day missing or Jan 01 if day and month are missing) and impute stop date as the latest date possible (i.e., last day of month if day is missing or Dec 31 if day and month are missing), then: If stop date < start date of study drug: PRIOR If stop date ≥ start date of study drug and start date ≤ end of study: CONCOMITANT If stop date ≥ start date of study drug and start date > end of study: POSTTREATMENT
	Missing	No PRIOR assignment if stop date is missing Impute start date as the earliest date possible (i.e., first day of month if day is missing or Jan 01 if day and month are missing), then: If start date ≤ end of study: CONCOMITANT If start date > end of study: POSTTREATMENT
CM Start Date	**CM Stop Date**	**Algorithms**

Missing	Known	No POSTTREATMENT assignment if start date is missing If stop date < start date of study drug: PRIOR If stop date ≥ start date of study drug: CONCOMITANT
	Partial	No POSTTREATMENT assignment if start date is missing Impute stop date as the latest date possible (i.e., last day of month if day missing or Dec 31 if day and month are missing), then: If stop date < start date of study drug: PRIOR If stop date ≥ start date of study drug: COMCOMITANT
	Missing	CONCOMITANT