J2J-MC-JZLD Statistical Analysis Plan Status Version 2

Evaluation of the Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Child-Bearing Potential

NCT04840888

Approval Date: 10-Nov-2021

STATISTICAL ANALYSIS PLAN

Evaluation of the Effect of Food, Omeprazole, Itraconazole, and Carbamazepine on the Pharmacokinetics of LY3484356 in Healthy Females of Non-Child-Bearing Potential

Statistical Analysis Plan Status: Version 2 Final
Statistical Analysis Plan Date: 10 November 2021

Study Drug: LY3484356

Sponsor Reference: J2J-MC-JZLD
Covance CRU Study: 1000071-8463112

Clinical Phase I

Approval Date: 10-Nov-2021 GMT

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2. ABBREVIATIONS

Abbreviations pertain to the Statistical Analysis Plan (SAP) only (not the tables, figures and listings [TFLs]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-12)	Area under the concentration versus time curve during one dosing interval of 12 hours
AUC(0-24)	Area under the concentration versus time curve from time zero to 24 hours postdose
BID	Twice daily
BQL	Below the quantifiable lower limit of the assay
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CL_{SS}/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable drug concentration
C_{max}	Maximum observed drug concentration
CRU	Clinical Research Unit
CSR	Clinical Study Report
C-SSRS	Columbia Suicide-Severity Rating Scale
CV	Coefficient of variation
DDI	Drug-drug interaction
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IP	Investigational product
MedDRA	Medical Dictionary for Regulatory Activities
MR_{AUC}	Metabolic ratio based upon AUC

PK	Pharmacokinetic
PPI	Proton pump inhibitor
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state after extravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration
WHO	World Health Organization

INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 05 March 2021), Clinical Study Protocol (a) (final version dated 03 September 2021), and Clinical Study Protocol (b) (final version dated 06 October 2021).

This SAP describes the planned analysis of the safety, tolerability and pharmacokinetic (PK) data from this study. A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical and PK analyses of data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement with Eli Lilly and Company. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. For open-label studies, this SAP must be signed off prior to first participant visit for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon with Eli Lilly and Company and identified in the CSR. Any minor deviations from the TFLs may not be documented in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

3. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the effect of food on the PK of LY3484356 after a low-fat meal in healthy females of non-childbearing potential	• Area under the concentration versus time curve from time zero to infinity [AUC(0-∞)], maximum observed drug concentration (C_{max}), and time of maximum observed drug concentration (t_{max}) of LY3484356
• To assess the effect of a gastric pH change on the PK of LY3484356 after multiple doses of a proton pump inhibitor (PPI) (omeprazole) in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, and t_{max} of LY3484356
• Assess the effect of coadministration of LY3484356 given as a single dose (DDI [drug-drug interaction] victim), with itraconazole, on the PK of LY3484356 in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, and t_{max} of LY3484356
• Assess the effect of coadministration of LY3484356 given as a single dose (DDI victim) with carbamazepine, on the PK of LY3484356 in healthy females of non-childbearing potential	• AUC(0-∞), C_{max}, and t_{max} of LY3484356
Secondary	
• To evaluate the safety and tolerability of single CCI [redacted] doses of LY3484356 in healthy females of non-childbearing potential	• Incidence and severity of adverse events (AEs) and serious adverse events (SAEs)
Exploratory	
• Assess the PK of carbamazepine and carbamazepine 10,11-epoxide	• C_{max} and AUC of carbamazepine and carbamazepine 10,11-epoxide
• Investigate the impact of coadministration of carbamazepine on the PK of midazolam	• C_{max} and AUC of midazolam and 1'-hydroxymidazolam with and without carbamazepine
• Assess exosomal mRNA in plasma	• Exosomal mRNA in plasma

4. STUDY DESIGN

Study J2J-MC-JZLD is an open-label, 5-cohort, study comprising 4 fixed-sequence crossover cohorts, and 1 randomized (1:1), 2-period crossover cohort. Cohorts 1 to 4 are in healthy females of non-childbearing potential to investigate the safety, tolerability, and PK of LY3484356 when administered as a single CCI [redacted], when dosed with and without food, and in the presence of omeprazole, or carbamazepine, and when administered as a single CCI [redacted] oral dose

when dosed in the presence of itraconazole. Optional and exploratory Cohort 5 is in healthy participants (males and non-pregnant and non-lactating females) to investigate the PK of the sensitive CYP3A substrate midazolam (and 1'-hydroxymidazolam) when dosed at various times in the presence of carbamazepine.

All participants will be screened within 28 days prior to enrollment. Details of each cohort's study design is below. Participants will attend a follow-up visit 7 to 10 days after discharge from the clinical research unit (CRU).

4.1 Cohort 1 (Food Effect)

Cohort 1 will be an open-label, randomized, crossover design evaluating the effect of food on LY3484356. Eligible participants will take place in 2 treatment periods. Participants will be admitted to the CRU on Day -1. On Day 1 of Treatment Period 1, participants will be randomized (1:1) to 1 of 2 treatment sequences; fasted/fed or fed/fasted. All participants will receive (according to the randomization schedule):

CCI

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 5 of Treatment Period 2.

Figure 1: J2J-MC-JZLD Study Schema - Cohort 1 (Food Effect)

4.2 Cohort 2 (PPI Effect)

Cohort 2 will be an open-label, fixed sequence design evaluating the effect of PPI on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

CCI

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 14.

Figure 2: J2J-MC-JZLD Study Schema - Cohort 2 (PPI Effect)

4.3 Cohort 3 (Itraconazole DDI)

Cohort 3 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of itraconazole on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 17.

Figure 3 below illustrates the study design for Cohort 3.

Figure 3: J2J-MC-JZLD Study Schema - Cohort 3 (Itraconazole DDI)

4.4 Cohort 4 (Carbamazepine DDI)

Cohort 4 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on LY3484356. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

There will be a washout period of CCI between doses of LY3484356. All participants will remain resident in the CRU until discharge on Day 27.

Figure 4: J2J-MC-JZLD Study Schema - Cohort 4 (Carbamazepine DDI)

4.5 Cohort 5 (optional) (Carbamazepine DDI with Midazolam)

Cohort 5 will be an open-label, fixed sequence design evaluating a potential drug-drug interaction of carbamazepine on midazolam. Eligible participants will take place in 1 treatment period. Participants will be admitted to the CRU on Day -1. All participants will receive:

All participants will remain resident in the CRU until discharge on Day 15.

Figure 5 below illustrates the study design for Cohort 5.


CCI

5. TREATMENTS

The following is a list of the study treatment sequence names that will be used in the TFLs.

Cohort	Study Treatment Sequence Name	Treatment order in TFL
1	CCI	1
	CCI	2
2	CCI	3
3	CCI	4
4	CCI	5
5 (optional)	CCI	6

BID = twice daily, QD = once daily

The following is a list of the study treatment names that will be used in the TFLs.

Cohort	Study Treatment Name	Treatment order in TFL
1	CCI	1
	CCI	2
2	CCI	3
	CCI	4
	CCI	5
3	CCI	6
	CCI	7
	CCI	8
4	CCI	9
	CCI	10
	CCI	11
	CCI	12
	CCI	13
5 (optional)	CCI	14
	CCI	15
	CCI	16
	CCI)	17
	CCI	18
	CCI	19
	CCI	20

[a] 200 mg itraconazole administered twice on Day 5 (loading dose), [b] 200 mg LY3484356 administered on Day 10 only, [c] 400 mg LY3484356 administered on Day 18 only, BID = twice daily, QD = once daily

6. SAMPLE SIZE JUSTIFICATION

In Cohorts 1 and 2, approximately 10 participants will be enrolled in each cohort to ensure that at least approximately 8 evaluable participants in each cohort, complete the study. The sample size (N=8) will provide at least 80% power that the 90% confidence interval (CI) of the ratio is included in the acceptance interval between 0.7 and 1.43, assuming that the expected geometric mean ratio is 1 and CCI [redacted]

In Cohort 3, approximately 20 participants will be enrolled to ensure that at least approximately 18 evaluable participants complete the study. In Cohort 4, approximately 26 participants will be enrolled to ensure that at least approximately 18 evaluable participants in this cohort complete the study. The sample size (N=18) will provide at least 80% power that the 90% CI of the ratio is included in the acceptance interval between 0.8 and 1.25, assuming that the expected geometric mean ratio is 1 and CCI [redacted]

In Cohort 5 (optional), approximately 15 participants will be enrolled to ensure that at least approximately 10 evaluable participants in this cohort complete the study.

7. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled participants who received at least one dose of investigational product (IP), whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all participants who received at least one dose of IP and have evaluable PK data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an AE of vomiting that occurs at or before 2 times median t_{max}.

All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when participants are assigned to analysis populations.

8. STATISTICAL METHODOLOGY

8.1 General

Data listings will be provided for all data that is databased. Summary statistics and statistical analysis will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum, maximum and n; for log-normal data (e.g. the PK parameters: AUCs and C_{max}) the geometric mean and geometric coefficient of variation will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual participants' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual participant's baseline value from the value at the timepoint. The individual participant's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

8.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

8.3 Pharmacokinetic Assessment

8.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1 or later) for the plasma concentrations of LY3484356 (Cohorts 1 to 4), and midazolam and 1'-hydroxymidazolam (Cohort 5) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
AUC(0-24)	ng.h/mL	area under the concentration versus time curve from time zero to 24 hours postdose (for midazolam only)
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (for LY3484356 and midazolam only)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (for LY3484356 and midazolam only)
V_{SS}/F	L	apparent volume of distribution at steady state after extra-vascular administration (for LY3484356 and midazolam only)
MR_{AUC}	NA	metabolic ratio based upon AUC (for midazolam and 1'-hydroxymidazolam only) $$\text{MRAUC} = \frac{Metabolite\ AUC}{Parent\ AUC}$$

The PK parameter estimates will be determined for plasma concentrations of carbamazepine and carbamazepine 10,11-epoxide (Cohorts 4 and 5) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration (final carbamazepine dosing day only)
AUC(0-12)	ng.h/mL	area under the concentration versus time curve during one dosing interval of 12 hours
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis (final carbamazepine dosing day only)
CLss/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (final carbamazepine dosing day only)
MR_{AUC}	NA	metabolic ratio based upon AUC(0-12) $\text{MRAUC} = \frac{Metabolite\ AUC}{Parent\ AUC}$

Plasma concentrations of itraconazole, carbamazepine, and midazolam, and their metabolites in Cohorts 3, 4, and 5 will be summarized using standard descriptive statistics as appropriate.

Additional PK parameters may be calculated, as appropriate.

The software and version used for the final analyses will be specified in the CSR. Any exceptions or special handling of data will be clearly documented within the final CSR.

Formatting of tables, figures and abbreviations will follow the Eli Lilly Global PK/PD/TS Tool: NON-COMPARTMENTAL PHARMACOKINETIC STYLE GUIDE. The version of the tool effective at the time of PK analysis will be followed.

General PK Parameter Rules

- Actual sampling times will be used in the final analyses of individual PK parameters, except for non-bolus pre-dose sampling times which will be set to zero. For non-bolus, multiple dose profiles, the pre-dose time will be set to zero unless a time deviation falls outside of the protocol blood collection time window which is considered to impact PK parameter derivation.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification, with at least one of these concentrations following C_{max}.

- AUC(0-∞) values where the percentage of the total area extrapolated is more than 20% will be flagged. Any AUC(0-∞) value excluded from summary statistics will be noted in the footnote of the summary table.

- Half-life ($t_{1/2}$) will be calculated, when appropriate, based on the apparent terminal log-linear portion of the concentration-time curve. The start of the terminal elimination phase for each participant will be defined by visual inspection and generally will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. Half-life will only be calculated when a reliable estimate for this parameter can be obtained comprising of at least 3 data points. If $t_{1/2}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

- A uniform weighting scheme will be used in the regression analysis of the terminal log-linear portion of the concentration-time curve.

- The parameters based on predicted last quantifiable drug concentration (C_{last}) will be reported (except in bioequivalence and bioavailability studies, where only the observed parameters will be reported).

Individual PK Parameter Rules

- Only quantifiable concentrations will be used to calculate PK parameters with the exception of special handling of certain concentrations reported below the lower limit of quantitation (BQL). Plasma concentrations reported as BQL will be set to a value of zero when all of the following conditions are met:

    - The compound is non-endogenous.

    - The samples are from the initial dose period for a participant or from a subsequent dose period following a suitable wash-out period.

    - The time points occur before the first quantifiable concentration.

- All other BQL concentrations that do not meet the above criteria will be set to missing.

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further

quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final CSR.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final CSR.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

<u>Data within an Individual Profile</u>

A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For PK profiles during multiple dosing, the concentration of the pre-dose sample exceeds all measured concentrations for that individual in the subsequent post-dose samples.

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.

- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and n ≥ 6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values

Individual values excluded as outliers will be documented in the final CSR. Approval of the final CSR will connote approval of the exclusion.

8.3.2 Pharmacokinetic Statistical Methodology

The PK parameters will be evaluated to estimate food effect and DDIs (with omeprazole, itraconazole, or carbamazepine). Log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) will be evaluated separately in each cohort.

To estimate the food effect in Cohort 1, a linear mixed-effects model with period, sequence, and treatment as fixed effects and participant as a random effect will be used. All evaluable data will be included in the analysis.

Example SAS code for Cohort 1 food effect analysis:

```
proc mixed data=xxx alpha=0.1;
  by parameter;
  class period sequence treatment participant;
  model log_pk = period sequence treatment / ddfm=kr2 residual cl;
  random participant;
  lsmeans treatment / pdiff alpha=0.1;
  ods output lsmeans=lsm diffs=diff;
run;
```

The geometric least squares mean for each treatment, geometric least squares mean ratios (fed versus fasted) and the corresponding 90% CI will be presented.

To estimate the effect of a gastric pH change in Cohort 2, and the following DDIs:

- LY3484356 with itraconazole (Cohort 3)
- LY3484356 with carbamazepine (Cohort 4)
- Midazolam with carbamazepine (Cohort 5),

log-transformed C_{max} and AUC(0-∞) parameters for LY3484356 (Cohorts 2, 3, and 4) and midazolam (Cohort 5) will be analyzed using a linear mixed-effects model with a fixed effect for treatment and a random effect for participant. These analyses will use similar SAS code to the above example, but with period removed from the model and class statements. The geometric least squares mean for each treatment, geometric least squares mean ratios (LY3484356 + omeprazole, itraconazole, or carbamazepine versus LY3484356 alone, and midazolam + carbamazepine versus midazolam alone) and the corresponding 90% CI will be presented.

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the difference between observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated for the same comparisons.

PK parameters will be summarized using descriptive statistics. Plasma concentrations of itraconazole, carbamazepine, and midazolam, and their metabolites in Cohorts 3, 4, and 5 will be summarized using standard descriptive statistics as appropriate.

8.4 Safety and Tolerability Assessments

8.4.1 Adverse events

Where changes in severity are recorded in the case report form, each separate severity of the AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to the first dose. A treatment-emergent adverse event (TEAE) is defined as an AE which occurs postdose or which is present prior to the first dose and becomes more severe postdose.

All AEs will be listed. TEAEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug by the investigator. Any SAEs will be listed. AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

8.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2020 B3), and listed.

8.4.3 Clinical laboratory parameters

For Cohort 1, all clinical chemistry and hematology data will be summarized by parameter, treatment, and timepoint, together with changes from baseline, where baseline is defined as Day -1 (of each treatment period for Cohort 1) assessment.

For Cohorts 2 to 5, all clinical chemistry and hematology data will be summarized by parameter, treatment sequence, and timepoint, together with changes from baseline, where baseline is defined as the Day -1 assessment.

These data, and urinalysis data will be listed. Additionally, clinical chemistry, hematology and urinalysis data outside the reference ranges will be listed and flagged on individual participant data listings.

8.4.4 Vital signs

For Cohort 1, vital signs data will be summarized by parameter, treatment, and timepoint, together with changes from baseline, where baseline is defined as the Day 1 predose (of each treatment period for Cohort 1) assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

For Cohorts 2 to 5, vital signs data will be summarized by parameter, treatment, and timepoint, together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment and timepoint.

Values for individual participants will be listed.

8.4.5 Electrocardiogram

ECGs will be performed for safety monitoring purposes only and will not be presented. Any clinically significant findings from ECGs will be reported as an AE.

8.4.6 Suicidal Ideation and Behavior Risk Monitoring

Participants in Cohort 5, being treated with carbamazepine, will be monitored appropriately and observed closely for suicidal ideation and behavior. The Columbia Suicide-Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire.

These data will be listed.

8.4.7 Hepatic Monitoring

If a participant experiences elevated laboratory parameters, as detailed in Section 8.2.6.1 of the protocol, additional tests will be performed to confirm the abnormality. Additional safety data may be collected if required, as defined in the protocol. Where applicable, the following will be presented.

The participants' liver disease history and associated person liver disease history data will be listed. Any concomitant medications that have potential for hepatotoxicity, including acetaminophen will be listed. Results from any hepatic monitoring procedures, such as a magnetic resonance elastography scan, and biopsy assessments will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by treatment and listed. Alcohol and recreational drug use data will also be listed.

All hepatic chemistry, hematology, coagulation, and serology data will be listed. Values outside the reference ranges will be flagged on the individual participant data listings.

8.4.8 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

8.4.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

9. INTERIM ANALYSES

An interim analysis of safety will be conducted after the completion of Cohorts 1 and 2. The interim analysis will be conducted to inform dosing restrictions in patient trials.

10. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

11. REFERENCES

1. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

12. DATA PRESENTATION

12.1 Derived Parameters

Individual derived parameters (e.g. PK parameters) and appropriate summary statistics will be reported to three significant figures. Observed concentration data, e.g. C_{max}, should be reported as received. Observed time data, e.g. t_{max}, should be reported as received. N and percentage values should be reported as whole numbers. Median values should be treated as an observed parameter and reported to the same number of decimal places as minimum and maximum values.

12.2 Missing Data

Missing data will not be displayed in listings.

12.3 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of participants or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

13. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.
Draft Version 2.0	10 November 2021	To reflect protocol amendments (a) and (b).

Leo Document ID = c97f2032-fbd7-4a27-b621-eba7551c7fc5

Approver: PPD

Approval Date & Time: 10-Nov-2021 15:44:59 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 10-Nov-2021 15:46:01 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 10-Nov-2021 16:08:30 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 10-Nov-2021 16:28:31 GMT

Signature meaning: Approved