J2A-MC-GZGH Statistical Analysis Plan version 1.0

A Phase 1 Multiple-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of 2 Different Formulations of LY3502970 in Healthy Participants

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STATISTICAL ANALYSIS PLAN

A Phase 1 Multiple-Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of 2 Different Formulations of LY3502970 in Healthy Participants

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1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-24)	Area under the concentration versus time curve from time zero to 24 hours
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
BQL	Below the limit of quantification
C_{last}	Last quantifiable drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
Frel(AUC)	Relative bioavailability based upon AUC(0-24)
Frel(C_{max})	Relative bioavailability based upon C_{max}
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PK	Pharmacokinetic
QD	Once daily
SAE	Serious adverse event

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

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 04 February 2022).

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].

4. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the PK of 2 different formulations of LY3502970 after multiple oral doses in healthy participants	• Maximum observed drug concentration (C_{max}), area under the plasma concentration-time curve from 0 to 24 hours [AUC(0-24)] and time of maximum observed concentration (t_{max})
Secondary	
• To assess the safety and tolerability of 2 different formulations of LY3502970 in healthy participants	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

5. STUDY DESIGN

Study GZGH is a Phase 1, single-site, randomized, open-label, crossover study conducted to assess PK, safety, and tolerability of 2 different formulations of LY3502970 in healthy participants.

Screening period

Screening may occur up to 42 days prior to enrollment.

Participants who are not enrolled within 42 days of screening may be subjected to an additional medical assessment with or without clinical measurements at the discretion of the investigator to confirm their eligibility.

Dose titration period (inpatient and outpatient visits)

There will be a dose titration period wherein participants will receive increasing doses of LY3502970 capsule for dose titration. Participants will be admitted in the Clinical Research Unit (CRU) on Day -1 and will undergo assessments until Day 2. Participants are planned to be discharged on Day 2 after receiving the study intervention. Within-treatment dose escalation will be every 7 days up to a dose of [redacted] mg once daily (QD) on Day 21. Participants will be provided take-home capsules for the remaining dose titration period. They will be required to visit the CRU on an outpatient basis during this period.

Test periods (inpatient)

Participants will be admitted in the CRU on Day 21 and will undergo assessments.

Participants will be randomly assigned to receive 2 different formulations of LY3502970. Serial blood samples for PK will be collected.

During Test Period 1 (Days 22 to 28), participants will receive 1 of the 2 different formulations of [redacted] mg LY3502970 capsules QD per randomization. They will crossover on Day 29 and will then receive the other formulation during Test Period 2 (Days 29 to 35).

Participants should follow local guidance and CRU precautions to minimize risk of coronavirus disease 2019 (COVID-19) infection. During this period, participants may be allowed to leave the CRU after completing the 2-hour fasting requirements postdose. However, they will be required to return to the CRU for overnight fasting on all days of test periods.

Participants are planned to be discharged on Day 36. However, the duration of stay in the CRU may be extended at the discretion of the investigator for safety or operational reasons.

Terminal PK period and safety follow-up visits

There will be a terminal PK period from Day 36 through the morning of Day 41 to collect additional PK samples following the final dose on Day 35.

Participants will complete the study after the safety follow-up visit, which will occur between 7 and 14 days after the last dose. Participants will undergo PK and safety assessments during this period.

6. TREATMENTS

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

Study Treatment Sequence Name	Abbreviation	Treatment Sequence order in TFL
[redacted] mg LY3502970 QD (Days [redacted]) / [redacted] mg LY3502970 QD (Days [redacted]) / [redacted] mg LY3502970 QD (Days [redacted]) / [redacted] mg LY3502970 QD (Formulation 1) (Days [redacted]) / [redacted] mg LY3502970 QD (Formulation 2) (Days [redacted])	[redacted] mg / [redacted] mg / [redacted] mg / [redacted] mg (Formulation 1) / [redacted] mg (Formulation 2) LY QD	1
[redacted] mg LY3502970 QD (Days [redacted]) / [redacted] mg LY3502970 QD (Days [redacted]) [redacted] mg LY3502970 QD (Days [redacted]) / [redacted] mg LY3502970 QD (Formulation 2) (Days [redacted]) / [redacted] mg LY3502970 QD (Formulation 1) (Days [redacted])	[redacted] mg / [redacted] mg / [redacted] mg / [redacted] mg (Formulation 2) / [redacted] mg (Formulation 1) LY QD	2

Abbreviations: Formulation 1 = nominal particle size spray-dried dispersion; Formulation 2 = large particle size spray-dried dispersion; QD = once daily

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

Study Treatment Name	Treatment order in TFL
[redacted] mg LY3502970 QD	1
[redacted] mg LY3502970 QD	2
[redacted] mg LY3502970 QD	3
[redacted] mg LY3502970 QD (Formulation 1)	4
[redacted] mg LY3502970 QD (Formulation 2)	5

Abbreviations: Formulation 1 = nominal particle size spray-dried dispersion; Formulation 2 = large particle size spray-dried dispersion; QD = once daily

The following is a list of the study treatment abbreviations that will be used in the Non-AE TFLs.

Study Treatment Name	Treatment order in TFL
[redacted] mg[redacted] mg/[redacted] mg LY3502970 QD	1
[redacted] mg LY3502970 QD (Formulation 1)	2
[redacted] mg LY3502970 QD (Formulation 2)	3

Abbreviations: Formulation 1 = nominal particle size spray-dried dispersion; Formulation 2 = large particle size spray-dried dispersion; QD = Once daily

7. SAMPLE SIZE JUSTIFICATION

This study is a multiple-dose study to investigate the PK, safety, and tolerability of 2 different formulations of LY3502970 in healthy participants. The sample size is based on a calculation of precision of the estimated ratio of AUC_{0-24} between [redacted]-mg capsule LY3502970 Formulation 1 and [redacted]-mg capsule LY3502970 Formulation 2. [redacted]

CCI , a sample size of 24 completed participants will provide approximately 90% coverage probability to get a 90% confidence internal (CI) for the ratio R of geometric mean AUC_{0-24} between treatments which will be within [0.899*R, 1.112*R].

Approximately 38 participants will be randomly assigned to study intervention such that approximately 24 evaluable participants complete the study. If a participant does not complete all the treatment periods of the study, they may be replaced by another participant if decided by the sponsor. This replacement participant will go through the same treatment sequence as the discontinued participant.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Entered" population will consist of all participants who sign the informed consent form.

The "Enrolled" population will consist of all participants who are assigned to treatment.

The "Safety" population will consist of all participants who are exposed to study intervention. Participants will be analyzed according to the intervention they actually received.

The "PK" population will consist of all enrolled participants who received LY3502970 and have evaluable PK samples.

All protocol deviations, including those due to COVID-19 and related restrictions 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.

9. STATISTICAL METHODOLOGY

9.1 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 SD, median, minimum, maximum and n; for log-normal data (e.g. the PK parameters: area under the concentration versus time curves [AUCs] and C_{max}) the geometric mean and geometric coefficient of variation (CV%) 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.

9.2 Demographics and Participant Disposition

Participant disposition will be summarized and listed. The demographic variables age, sex, race, ethnicity, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental methods in validated software program, Phoenix WinNonlin (Certara, Version 8.1.1 or later).

Plasma concentrations of LY3502970 will be used determine the following PK parameters where 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(0-24)	ng.h/mL	Area under the concentration versus time curve from time zero to 24 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 (λ_z) in non-compartmental analysis
CL/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
Frel(AUC)		Relative bioavailability based upon AUC(0-24)
Frel(C_{max})		Relative bioavailability based upon C_{max}

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 pre-dose sampling times which will be set to zero.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one-time point, 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}.

- 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.

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 quantification (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.

- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be C_{min} for the dosing interval.

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 study report.

- 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 of ± 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 study report.

Treatment of Outliers during PK 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 report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

All PK parameters will be listed and summarized using descriptive statistics.

The primary parameters for analysis of LY3502970 will be AUC(0-24), C_{max}, and t_{max}. The data for AUC(0-24) and C_{max} from Test Periods 1 and 2 will be log-transformed. The log-transformed data will be analyzed using a linear mixed-effects model with treatment CCI mg capsule LY3502970 Formulation 1, CCI mg capsule LY3502970 Formulation 2), period and sequence as fixed effects, and participant within sequence as a random effect. The ratios of the geometric

least square means and the 90% CIs for the ratios will be derived for [CCI] mg capsule LY3502970 Formulation 2 versus [CCI] mg capsule LY3502970 Formulation 1.

Example of SAS code as follows (where [CCI] mg capsule LY3502970 Formulation 1 is coded as trtan=1, this will be updated in the actual SAS code to reflect the actual coding of trtan):

```
proc mixed data = <data in>;
by parcat1n parcat1 paramn param;
class trtan aperiod trtseqp usubjid;
model lpk = trtan aperiod trtseqp / cl residual ddfm = kr2;
lsmeans trtan / cl pdiff = control ('1') alpha = 0.1;
random intercept / participant = usubjid(trtseqp);
ods output lsmeans = <data out>;
ods output diffs = <data out>;
run;
```

The t_{max} will be analyzed using the Wilcoxon signed-rank test. The median for each treatment, the median difference between the Formulation 2 and Formulation 1 treatments, and corresponding approximate 90% CI will be calculated.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (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 a condition 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 dosing. A treatment-emergent AE is defined as an AE which occurs postdose or which is present prior to dosing and becomes more severe postdose.

All AEs will be listed. Treatment-emergent AEs 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 treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 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 serious AEs will be listed. AEs by day of onset will be presented.

Discontinuations due to AEs will be listed.

Nausea, vomiting, diarrhoea and acute pancreatitis will be listed as adverse events of special interest (AESIs).

Other additional AESIs will be listed.

9.4.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments.

Hypoglycemic events will be appropriately recorded in the CRF. In the case of a hypoglycemic event, the actual blood glucose value, if measured, will be recorded in the CRF, together with any treatments administered. Each category of hypoglycemic events (defined below) will be listed and summarized by treatment. Hypoglycemia is defined as follows:

- **Level 1 hypoglycemia:**
  - Glucose <70 mg/dL [3.9 mmol/L] and ≥54 mg/dL [3.0 mmol/L] - It can alert a person to take action, such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

- **Level 2 hypoglycemia:**
  - Glucose <54 mg/dL [3.0 mmol/L] - This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.

- **Level 3 hypoglycemia:**
  - Severe hypoglycemia [in adults] - A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- **Other hypoglycemia categories:**
  - Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that occurs at night and presumably during sleep.

Investigator review of glucose results clinically indicative of hypoglycemia will be required.

9.4.3 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version B3 September 2021). Concomitant medication will be listed.

9.4.4 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, treatment and timepoint, and also listed. 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.

9.4.5 Vital signs

Vital signs data will be summarized by treatment 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 timepoint.

Values for individual participants will be listed.

9.4.6 Electrocardiogram (ECG)

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.

9.4.7 Hepatic Monitoring

Close hepatic monitoring

If a participant who had normal or near normal baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin (TBL) (i.e., <1.5× upper limit of normal [ULN]), experiences elevated ALT≥3× ULN, AST≥3× ULN, ALP≥2× ULN, or TBL≥2× ULN (except for participants with Gilbert's syndrome), laboratory tests should be repeated within 48 to 72 hours, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing.

In participants enrolled with elevated baseline ALT, AST, ALP or TBL (≥1.5× ULN), the thresholds for close monitoring are ALT≥2× baseline, AST≥2× baseline, ALP≥2× baseline, or TBL≥1.5× baseline (except for participants with Gilbert's syndrome).

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses, (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Comprehensive hepatic evaluation

If a study participant, who had baseline ALT, AST, ALP, TBL<1.5× ULN, experiences elevated ALT≥5× ULN, AST≥5× ULN, ALP ≥3× ULN, TBL ≥2× ULN (except for participants with Gilbert's syndrome), or elevated ALT, AST ≥3× ULN with hepatic signs/symptoms (severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia>5%), a comprehensive evaluation should be performed to search for possible causes of liver injury.

In participants who had elevated baseline ALT, AST, ALP, or TBL (≥1.5× ULN), the thresholds for performing this evaluation are ALT≥3× baseline, AST≥3× baseline, ALP≥2× baseline, TBL≥2× baseline (except for participants with Gilbert's syndrome), or ALT, AST ≥2× baseline with hepatic signs/symptoms.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio, viral hepatitis A, B, C, or E, tests for autoimmune hepatitis, and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Additional hepatic data collection in participants who have abnormal liver tests during the study

Additional hepatic safety data collection should be performed in participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5× ULN on 2 or more consecutive blood tests (if baseline ALT<1.5x ULN)
   - In participants with baseline ALT≥1.5× ULN, the threshold is ALT≥3x baseline on 2 or more consecutive tests

2. Elevation of TBL to ≥2× ULN (if baseline TBL <1.5× ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2x baseline.

3. Elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests (if baseline ALP <1.5× ULN)
   - In participants with baseline ALP≥1.5× ULN, the threshold is ALP ≥2× baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be a serious AE

5. Discontinuation of the investigational product due to a hepatic event

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.

9.4.8 Pancreatic Safety

If a participant is suspected of having acute pancreatitis (including, elevated serum amylase or lipase values ≥3× ULN), additional monitoring and tests will be performed to confirm the abnormality, even in asymptomatic participants.
All serum amylase and lipase data will be summarized by treatment, and listed.

9.4.9 Other assessments

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

9.4.10 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim statistical analyses are planned.

11. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

12. 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.

13. DATA PRESENTATION

13.1 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.

13.2 Missing Data

Missing data will not be displayed in listings.

13.3 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.”

14. APPENDICES

Appendix 1: Document History

Status and Version	Date of Change	Summary/Reason for Changes
Final Version 1.0	NA	NA; the first version.

NA = not applicable

Leo Document ID = 7a224dcb-6de4-435b-b65d-acf8299e2c9f

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Signature meaning: Approved

Approver: PPD

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