Statistical Analysis Plan Version 1 J2A-MC-GZGK

A Multiple Dose Study in Healthy Overweight and Obese Participants to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3502970

NCT05313802

Approval Date: 25-Mar-2022

STATISTICAL ANALYSIS PLAN

A Multiple Dose Study in Healthy Overweight and Obese Participants to Investigate the Safety, Tolerability, and Pharmacokinetics of LY3502970

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Version: 1.0
Statistical Analysis Plan Date: 22MAR2022

Investigational Medicinal Product: LY3502970

Protocol Reference: J2A-MC-GZGK
Labcorp Drug Development Study: 8491855

Clinical Phase I

Approval Date: 25-Mar-2022 GMT

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

% AUC_{extrap}	Fraction of AUC(0-∞) extrapolated
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
AUCτ	Area under the concentration-time curve during one dosing interval
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
BQL	Below the limit of quantification
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last predicted observed drug concentration
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
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PD	Pharmacodynamic
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_{last}	Last time point where the concentration is above the limit of quantitation
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
VAS	Visual analog scale
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 25 January 2022) and Protocol Amendment (a) (final version dated 21 February 2022).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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. 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

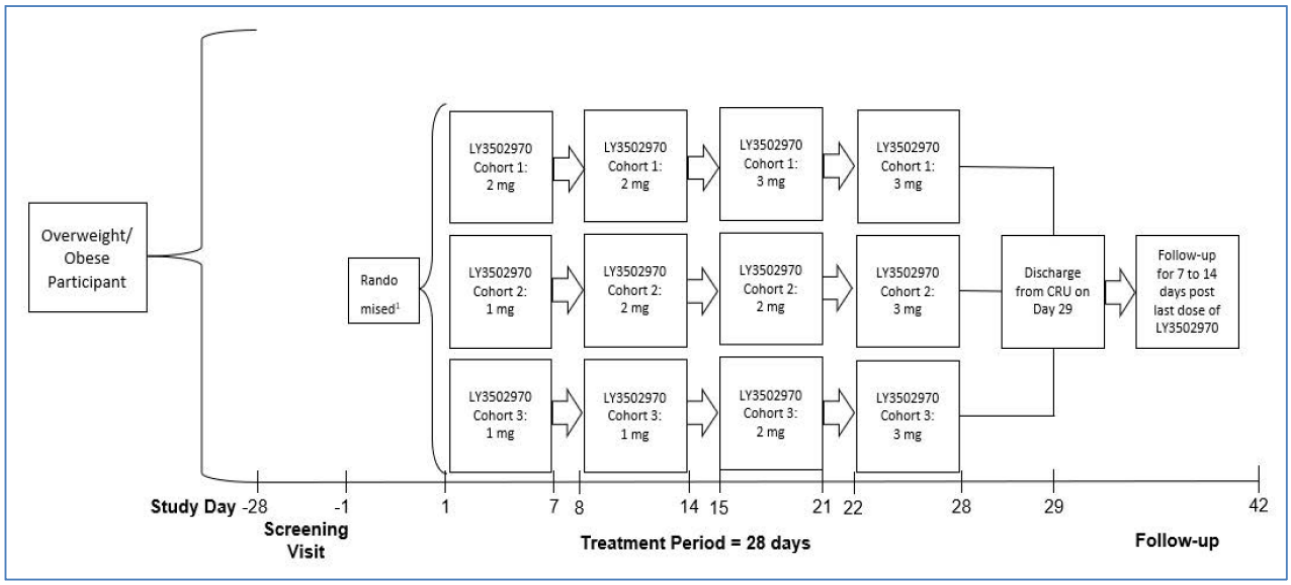
Objectives	Endpoints
Primary	
• To evaluate the safety and tolerability of different dosing regimens	• Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
Secondary	
• To characterize the PK of multiple doses of LY3502970 • To evaluate the PD of different dosing regimens of LY3502970	• Maximum observed drug concentration (C_{max}), area under the concentration versus time curve (AUC) and time of maximum observed concentration (t_{max}) • Weight change from baseline to 4 weeks and change in appetite (Visual Analogue Scale [VAS] scores)

5. STUDY DESIGN

Study GZGK is a Phase 1, multi-center, randomized, investigator and participant-blind, multiple

dose study in healthy obese and overweight participants.

Study Schema



Screening Period

Screening may occur within 28 days of the first dose of LY3502970. Participants who are not enrolled within 28 days of screening may be subjected to an additional medical assessment with or without clinical measurements to confirm their eligibility.

Randomization

A maximum of 72 participants will be randomly assigned to three treatment arms with a randomization ratio of 1:1:1 such that approximately 60 evaluable participants complete the study.

Study visits

The study will include the following visits:

- Treatment period: 28 days
  - Participants will be admitted to the Clinical Research Unit (CRU) on Day -1 and will undergo assessments
  - Participants are planned to be discharged on Day 29. However, the duration of stay in the CRU may be extended at the discretion of the investigator for safety or operational reasons.
  - Participants will receive single oral doses of LY3502970 from Day 1 until Day 28.
- Follow-up: 7 to 14 days post last dose of LY3502970
- Participants should follow local guidance and CRU precautions to minimize risk for coronavirus disease 2019 (COVID-19) infection.

Participant replacement

Replacement allowed if:

- Participant is randomized but not administered treatment. This is to ensure enough participants complete the study.
- Participant does not complete the entire treatment period of the study. This replacement is at the discretion of the sponsor.

Replacement not allowed if:

- Participant is withdrawn from the study due to safety reasons deemed related to LY3502970.

6. TREATMENTS

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

Cohort	Study Treatment Sequence Name	Treatment Sequence order in TFL
1	2 mg (Days 1 – 14) / 3 mg (Days 15 – 28) LY3502970 QD	1
2	1 mg (Days 1 – 7) / 2 mg (Days 8 – 21) / 3 mg (Days 22 – 28) LY3502970 QD	2
3	1 mg (Days 1 – 14) / 2 mg (Days 15 – 21) / 3 mg (Days 22 – 28) LY3502970 QD	3

Abbreviation: QD = once daily

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

Cohort	Study Treatment Name	Treatment order in TFL
1	2 mg LY3502970 QD	1
	3 mg LY3502970 QD	2
2	1 mg LY3502970 QD	3
	2 mg LY3502970 QD	4
	3 mg LY3502970 QD	5
3	1 mg LY3502970 QD	6
	2 mg LY3502970 QD	7
	3 mg LY3502970 QD	8

Abbreviation: QD = once daily

7. SAMPLE SIZE JUSTIFICATION

Approximately 72 participants will be randomized such that 60 participants will complete the study (24 participants enrolled per arm for 20 completers participants per arm). The sample size is customary for Phase 1 studies evaluating safety and tolerability parameters and is considered sufficient to evaluate the primary objective of this study.

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 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 "Pharmacokinetic" 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 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 (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, country of enrolment, site ID, body weight, height, body mass index, HbA1c and fasting glucose (if data available) will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The following PK parameters will be determined where possible from the plasma concentrations of LY3502979 using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

PK Parameters of Single dose on PK profile Day 1 and of Multiple dose on PK profile Day 28

Parameter	Units[a]	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
AUCτ	ng.h/mL	area under the concentration-time curve during one dosing interval
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from zero to infinity (Day 28 only)
%AUC_{extrap}	%	fraction of AUC(0-∞) extrapolated (Day 28 only)
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
t_{last}	h	last time point where the concentration is above the limit of quantitation
$t_{1/2}$	h	half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis (Day 28 only)
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

The planned dosing interval τ is 24 hours
[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.

Additional PK parameters may be determined where 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.

- 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}.

- The $t_{1/2}$ 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 last observed 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.

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 in 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.

Data within an Individual Profile

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

- 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.

9.3.2 Pharmacokinetic Statistical Methodology

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

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Effect of LY3502970 on body weight will be evaluated, Body weight data will be summarized by cohort and timepoint together with change from baseline, where baseline is defined as the Day 1 predose assessment.

Overall appetite score is measured using a 100-mm validated VAS. The data will be listed and summarized by cohort and timepoint together with changes from baseline, where baseline is defined as the Day -1 assessment.

Body weight and overall appetite data for individual participants will be listed.

9.5 Safety and Tolerability Assessments

9.5.1 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 cohort and 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 cohort and 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.

Summaries for incidence and severity of GI TEAEs (nausea, vomiting, diarrhea, constipation, nausea and vomiting combined, and all 4 events combined), will be provided by week and by cohort. In addition, the tolerability of 1 mg during the first week will also be evaluated through a summary combining data in Week 1 for all participants from cohort 2 and cohort 3. The number of participants with GI TEAEs will be plotted by week and cohort and for overall.

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

Other additional AESIs also listed.

9.5.2 Concomitant medication

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

9.5.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter, along with changes from baseline, where baseline is the Day 1 predose assessment, and 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.

9.5.4 Vital signs

Vital signs data will be summarized by cohort 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 timepoints.

Values for individual participants will be listed.

9.5.5 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.

9.5.6 Hepatic Monitoring

Close hepatic monitoring

If a study 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).

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.

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.

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

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 cohort 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.

9.5.7 Other assessments

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

9.5.8 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 = 8f01279a-02a8-4abd-973c-8731db4b6d75

Approver: PPD

Approval Date & Time: 22-Mar-2022 16:13:01 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 22-Mar-2022 16:21:10 GMT

Signature meaning: Approved

Approver:PPD

Approval Date & Time: 23-Mar-2022 18:13:36 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 25-Mar-2022 21:10:05 GMT

Signature meaning: Approved