

J2A-MC-GZGJ Statistical Analysis Plan v1

A Phase 1 Multiple Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of LY3502970 in Fed and Fasted Healthy Participants

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STATISTICAL ANALYSIS PLAN

A Phase 1 Multiple Dose Study to Investigate the Pharmacokinetics, Safety, and Tolerability of LY3502970 in Fed and Fasted Healthy Participants

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2. ABBREVIATIONS

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

AE	Adverse event
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 postdose
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 quantifiable lower limit of the assay
C _{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
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
LS	Least square
MedDRA	Medical Dictionary for Regulatory Activities
PG	Plasma Glucose
PK	Pharmacokinetic
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
SOP	Standard Operating Procedure
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_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 26 July 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 Trials¹ and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of CSRs².

4. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
<ul style="list-style-type: none">To characterize and compare the PK of LY3502970 after multiple oral doses in the fasted and fed state in healthy participants	<ul style="list-style-type: none">Maximum observed drug concentration (C_{max}), area under the concentration versus time curve from time zero to 24 hours postdose (AUC_{0-24}) and time of maximum observed drug concentration (t_{max})
Secondary	
<ul style="list-style-type: none">To assess the safety and tolerability of LY3502970 in healthy participants	<ul style="list-style-type: none">Incidence of treatment emergent adverse events (TEAEs) and serious adverse events (SAEs)

5. STUDY DESIGN

Study GZGJ is a Phase 1, single site, randomized, open label, crossover study that will be conducted to assess PK, safety, and tolerability of LY3502970 in healthy participants in fed and fasted state.

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 to confirm their eligibility.

Dose Titration Period (Inpatient and Outpatient Visits)

There will be a dose titration period where participants will receive increasing doses of LY3502970 CCI 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 16 mg QD on Day 22. Participants will be provided take-home CCI 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. Participants will be randomized to receive study intervention under 2 administration conditions (fed state or fasted state). In the fed part of test periods, participants will be administered a high fat, high-calorie meal on the last day of dosing with LY3502970, and serial blood samples for PK will be collected.

During the test period 1 (Days 22 to 28), participants will receive 16 mg LY3502970 CCI QD either in the fed or fasted state as per randomization. They will crossover on Day 29 and will then receive the study intervention under the other administration condition during test period 2 (Days 29 to 35).

Participants should follow local guidance and CRU precautions to minimize risk for coronavirus disease 2019 (COVID-19) infection. During this period, participants may be allowed to leave the CRU after completing the 4-hour fasting requirements post dosing. However, they would 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 Pharmacokinetics 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 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
2 mg LY QD (Days 1-7) / 4 mg LY QD (Days 8-14) / 8 mg LY QD (Days 15-21) / 16 mg LY QD (fed) (Days 22-28) / 16 mg LY QD (fasted) (Days 29-35)	2 mg/4 mg/8 mg/16 mg fasted/16mg fed LY QD	1
2 mg LY QD (Days 1-7) / 4 mg LY QD (Days 8-14) / 8 mg LY QD (Days 15-21) / 16 mg LY QD (fasted) (Days 22-28) / 16 mg LY QD (fed) (Days 29-35)	2 mg/4 mg/8 mg/16 mg fed/16mg fasted LY QD	2

Abbreviation: LY: LY3502970; 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
2 mg LY3502970 QD	1
4 mg LY3502970 QD	2
8 mg LY3502970 QD	3
16 mg LY3502970 QD (fasted)	4
16 mg LY3502970 QD (fed)	5

Abbreviation: QD: Once daily.

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

Study Treatment Name	Treatment order in TFL
2 mg/4 mg/8 mg LY3502970 QD	1
16 mg LY3502970 QD (fasted)	2
16 mg LY3502970 QD (fed)	3

7. SAMPLE SIZE JUSTIFICATION

This study is a pilot PK study to assess PK LY3502970 in healthy participants in fed and fasted state. The sample size is based on a calculation of precision of the estimated ratio of AUC₀₋₂₄ between 16 mg CCI LY3502970 fasted and 16 mg CCI LY3502970 fed. Assuming a standard deviation of treatment difference of 0.444 in the log-scale in AUC₀₋₂₄ (according to a preliminary analysis of the food effect data in Study GZGA), a sample size of 24 completed

participants will provide approximately 80% coverage probability to get a 90% CI for the ratio R of geometric mean AUC_{0-24} between treatments within $[0.767 \cdot R, 1.303 \cdot R]$.

Approximately 30 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 complete 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 participants who received LY3502970 and have evaluable PK samples.

All protocol deviations, including those due to coronavirus disease 2019 (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, 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

Noncompartmental methods applied with a validated software program (Phoenix WinNonlin Version 8.1 or later) will be used.

Plasma concentrations of LY3502970 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC ₍₀₋₂₄₎	ng.h/mL	area under the concentration versus time curve from time zero to 24 hours postdose
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 (Day 28 and 35 only)
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (Day 28 and 35 only)
V _z /F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (Day 28 and 35 only)

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.
- The parameters 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.

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.
- For multiple-dosing data, when pre-dose concentrations are missing, the value to be substituted will be the minimum observed drug concentrations 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 $\pm 10\%$, 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 $\pm 10\%$. 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.

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 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 $n \geq 6$, 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 $\pm 3 \times \text{SD}$ of the remaining log-transformed values.
 - d. If the extreme value is within the range of arithmetic mean $\pm 3 \times \text{SD}$, 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 $\pm 3 \times \text{SD}$, 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 $n \geq 6$ 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 $\pm 3 \times \text{SD}$ 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. PK parameter estimates for LY3502970 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis of LY3502970 will be AUC_{0-24} , C_{\max} , and t_{\max} . The data for AUC_{0-24} , C_{\max} from test period 1 and 2 will be log-transformed. The log-transformed data will be analyzed using a linear mixed-effects model with treatment (16 mg CCI LY3502970 fasted, 16 mg CCI LY3502970 fed), 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 16 mg CCI LY3502970 fed versus 16 mg CCI LY3502970 fasted.

Example of SAS code as follows (where 16 mg CCI LY3502970 fasted is coded as $\text{trtan}=1$, 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 / subject = usubjid(trtseqp);  
ods output lsmeans = <data out>;  
ods output diffs = <data out>;  
run;
```

The tmax will be analyzed using the Wilcoxon signed-rank test. The median for each treatment, the median difference between the fed and fasted 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 24.0 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).

9.4.2 Glucose Monitoring and Hypoglycemia

During the study, blood glucose concentrations will be monitored for safety assessments. Glucose data will be listed and summarized by treatment together with changes from baseline, where baseline is defined as Day 1 predose.

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:

- **Glucose Alert Level (Level 1):**

- 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.
- **Clinically Significant Hypoglycemia (Level 2):**
 - 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 or absence of symptoms of hypoglycemia.
- **Severe hypoglycemia (Level 3):**
 - 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 defined as any hypoglycemic event that occurs between bedtime and waking.

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

9.4.3 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 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 treatment.

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.

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., $<1.5\times$ upper limit of normal [ULN]), experiences elevated $ALT\geq 3\times$ ULN, $AST\geq 3\times$ ULN, $ALP\geq 2\times$ ULN, or $TBL\geq 2\times$ ULN, 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.

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, $TBL<1.5\times$ ULN, experiences elevated $ALT\geq 5\times$ ULN, $AST\geq 5\times$ ULN, $ALP\geq 3\times$ ULN, $TBL\geq 2\times$ ULN, or elevated ALT, $AST\geq 3\times$ 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.

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 $\geq 5\times$ ULN on 2 or more consecutive blood tests (if baseline $ALT<1.5\times$ ULN)

-
- In participants with baseline $ALT \geq 1.5 \times ULN$, the threshold is $ALT \geq 3 \times$ baseline on 2 or more consecutive tests
 - 2. Elevation of TBL to $\geq 2 \times ULN$ (if baseline TBL $< 1.5 \times ULN$)
 - In participants with baseline TBL $\geq 1.5 \times ULN$, the threshold should be TBL $\geq 2 \times$ baseline (except for cases of known Gilbert's syndrome)
 - 3. Elevation of serum ALP to $\geq 2 \times ULN$ on 2 or more consecutive blood tests (if baseline ALP $< 1.5 \times ULN$)
 - In participants with baseline ALP $\geq 1.5 \times ULN$, the threshold is ALP $\geq 2 \times$ 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 experiences elevated serum amylase or lipase values $\geq 3 \times ULN$, 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 Meals

Meal intake data during test period will be listed.

9.4.10 Other assessments

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

9.4.11 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