J2J-MC-JZLE Statistical Analysis Plan Version 1.0

An Open-label, Two-part Study of the Disposition and Absolute Bioavailability of [^{14}C]-LY3484356 in Healthy Females of Non-Childbearing Potential

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Approval Date: 21-Jul-2021

STATISTICAL ANALYSIS PLAN

An Open-label, Two-part Study of the Disposition and Absolute Bioavailability of [^{14}C]-LY3484356 in Healthy Females of Non-Childbearing Potential

Statistical Analysis Plan Status: Final
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Study Drug: LY3484356

Sponsor Reference: J2J-MC-JZLE
Covance CRU Study: 1001215-8468429

Clinical Phase I

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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]).

%AUC(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BQL	Below the quantifiable lower limit of quantitation
CL	Total body clearance of drug calculated after intra-vascular administration
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{last}	Last quantifiable concentration
C_{max}	Maximum observed drug concentration
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
F	Absolute bioavailability
ICH	International Conference on Harmonisation
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SD	Standard deviation
$t_{1/2}$	Half-life associated with the terminal rate constant (λ_z) in non-compartmental analysis
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state after intra-vascular administration
V_{ss}/F	Apparent volume of distribution at steady state after extravascular administration
V_z	Volume of distribution during the terminal phase after intra-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 25 May 2021), and Protocol Amendment (a) (final version dated 25 June 2021).

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

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

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

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

4. STUDY OBJECTIVES

Objectives	Endpoints
Primary	
Part 1 • To determine the disposition of radioactivity in healthy nonchildbearing women following oral administration of a single dose of CCI [^{14}C]-LY3484356 Part 2 • To determine the absolute bioavailability of LY3484356 following a single oral dose of CCI of LY3484356 along with an intravenous (IV) dose of CCI of [^{14}C]-LY3484356 (containing CCI	Part 1 • Urinary and fecal excretion of total radioactivity over time expressed as a percentage of the total radioactive dose Part 2 • Absolute bioavailability (F) of LY3484356
Secondary	
Part 1	Part 1

• To determine the PK of total radioactivity and LY3484356 in plasma following a single oral dose of CCI [^{14}C]-LY3484356	• Area under the concentration versus time curve from time zero to infinity (AUC[0-∞]) and maximum observed drug concentration (C_{max}) for radioactivity and LY3484356 in plasma
• To assess the mass balance by quantifying radioactivity excretion in urine, feces, and expired air (if applicable)	• Total radioactivity recovered in urine, feces, and expired air (if applicable)
• To identify metabolites of LY3485346 in plasma, urine, and feces	• Total number of metabolites and identification of metabolite
• To assess the safety and tolerability of a single dose of CCI [^{14}C]-LY3484356 CCI in healthy nonchildbearing women.	• A summary of treatment-emergent adverse events (TEAEs).
Part 2	Part 2
• To evaluate the PK of LY3484356, [^{14}C]-LY3484356, and total radioactivity following oral dosing of LY3484356 and IV dosing of [^{14}C]-LY3484356	• AUC(0-∞) and C_{max} for total radioactivity, [^{14}C]-LY3484356, and LY3484356 in plasma
• To assess the safety and tolerability of LY3484356 following a single oral dose of CCI LY3484356 along with an IV dose of CCI of [^{14}C]-LY3484356 CCI in healthy nonchildbearing women	• A summary of TEAEs.

5. STUDY DESIGN

5.1 Overall Design

Study JZLE is an open-label, 2-part, disposition and absolute bioavailability study of [^{14}C]-LY3484356 in healthy females with nonchildbearing potential at a single Phase 1 clinical research unit (CRU). In Part 1, it is planned that up to 6 participants may be enrolled to ensure that at least 4 participants complete the study or have evaluable PK data. In Part 2, it is planned that up to 8 participants may be enrolled to ensure that at least 6 participants complete the study or have evaluable PK data for both treatments (oral and IV). Participants in Part 1 will not participate in Part 2, nor will participants in Part 2 participate in Part 1. Part 1 and Part 2 are independent of each other and do not need to be conducted in sequential order.

Safety assessments, including adverse events (AEs), clinical laboratory tests, vital signs, and electrocardiogram (ECGs), and blood sampling for PK, will be performed.

A schematic of the study designs are presented in Figure 1 (Part 1) and Figure 2 (Part 2).

5.1.1 Screening (Part 1 and Part 2)

All participants will be screened within 28 days prior to enrolment.

5.1.2 Treatment and Assessment Period

Part 1

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 10 hours, participants will receive a single oral dose of CCI of [^{14}C]-LY3484356 CCI administered as an oral solution.

Participants will be discharged from the CRU as early as Day 12 and up to Day 22, provided recovery of radioactivity has reached the following threshold values:

- ≥90% of the radioactive dose is recovered, and
- ≤1% of the radioactive dose per day is recovered in excreta (urine and feces combined) for 2 consecutive days on which a fecal sample is collected.

Sample collection and CRU confinement will continue until discharge criteria are met or the maximum stay is reached, unless otherwise agreed upon by the sponsor and investigator (or designee).

For participants experiencing emesis within 4 hours following ^{14}C dosing, vomitus will be collected. Attempts will be made to collect vomitus from participants experiencing emesis after 4 hours post dose. All vomitus will be collected and stored for possible analysis as deemed appropriate.

Part 2

Participants will be admitted to the CRU on Day -1. On the morning of Day 1, following an overnight fast of at least 10 hours, participants will receive a single oral dose of CCI of LY3484356 as CCI tablets and followed 4 hours later by a single dose of CCI of [^{14}C]-LY3484356 (containing 1 μCi of radioactivity [microtracer]) administered as approximately CCI IV infusion. Participants will remain resident in the CRU until Day 9.

During the infusion and for at least 2 hours post-infusion, the blood samples will be taken from the arm contra-lateral to the infusion site.

5.1.3 Follow-up (Part 1 and Part 2)

Participants will receive a follow-up call approximately 7 days after clinic discharge.

6. TREATMENTS

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

Part	Study Treatment Name	Treatment order in TFL
1	CCI	1
2	CCI	2

7. SAMPLE SIZE JUSTIFICATION

No formal statistical assessment of sample size has been conducted as this study does not have a hypothesis. The sample size chosen for this study is common in human radiolabeled studies and is considered sufficient to achieve the objectives of the study. In Part 1, up to 6 participants may be enrolled to ensure that at least 4 participants complete the study or have evaluable PK data; in Part 2, up to 8 participants may be enrolled to ensure that at least 6 participants complete the

study or have evaluable PK data for both treatments (oral and IV). Each participant will participate in either Part 1 or Part 2. In the event of early withdrawal of any participants and/or to ensure the appropriate number of participants complete each part of the study, replacement participants may be enrolled at the discretion of the sponsor.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled participants who take at least 1 dose of LY3484356 or [^{14}C]-LY3484356, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all participants who received at least 1 dose of LY3484356 or [^{14}C]-LY3484356, and have evaluable PK data.

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

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: area under the concentration versus time curve [AUC] 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 listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized and listed. All other demographic variables will be listed only.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

The PK parameter estimates will be determined using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

Plasma total radioactivity concentrations, and plasma concentrations of LY3484356 (Part 2 only) and [^{14}C]-LY3484356 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL and ng equiv•h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	ng.h/mL and ng equiv•h/mL	area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL and ng equiv/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{1/2}$	h	half-life associated with the terminal rate constant (λz) in non-compartmental analysis
CL/F	L/h	apparent total body clearance of drug calculated after extra-vascular administration (LY3484356 and [^{14}C]-LY3484356 only)
CL	L/h	total body clearance of drug calculated after intra-vascular administration ([^{14}C]-LY3484356 only)
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (LY3484356 and [^{14}C]-LY3484356 only)
V_z	L	volume of distribution during the terminal phase after intra-vascular administration ([^{14}C]-LY3484356 only)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration (LY3484356 and [^{14}C]-LY3484356 only)
V_{ss}	L	volume of distribution at steady state after intra-vascular administration ([^{14}C]-LY3484356 only)
F	%	absolute bioavailability (Part 2 only)

Estimates of absolute bioavailability in Part 2 will be made as follows:

$$F\,\% = \frac{[\text{AUC}(0\text{-}\infty),\ \text{LY3484356}] \times [\text{Dose},\ [^{14}\text{C}]\text{-LY3484356}]}{[\text{AUC}(0\text{-}\infty),\ [^{14}\text{C}]\text{-LY3484356}\ ] \times [\text{Dose},\ \text{LY3484356}]} \times 100\%$$

Based on concentration data, the ratios of plasma LY3484356 to plasma total radioactivity will be calculated per time point in Part 1.

In addition, the ratios of exposure of plasma LY3484356 to plasma total radioactivity will be calculated based on AUC(0-∞) and C_{max}. An alternative AUC measure, such as AUC to a common time point, may be calculated if AUC(0-∞) cannot be reliably calculated.

Additional PK parameters may be calculated, as appropriate. The PK excretion data will be presented in the radioanalysis report.

The percentage and cumulative percentage of radiolabeled dose excreted in expired air may also be presented for Part 1, if applicable.

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 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}.

- The 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}.

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

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

$t_{1/2}$ value excluded from summary statistics will be documented in the footnote of the summary table.

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

- For Part A, parameters based on predicted last quantifiable concentration (C_{last}) will be reported, and for Part B, parameters based on observed 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 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 plasma 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 plasma 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 plasma concentration profiles will be graphed using scheduled (nominal) sampling times.

- The average plasma concentration profiles will be graphed using arithmetic average concentrations.

- The pre-dose average plasma 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.

- Plasma 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 plasma concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final CSR.

Treatment of Outliers during Pharmacokinetic Analysis

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

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 $n\geq6$, 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 $n \geq 6$ 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 ±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

No formal statistical analyses are planned.

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 AE will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the participant has provided written informed consent and is ongoing at consent. A non-treatment emergent AE is defined as an AE which starts after informed consent but prior to 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 part, 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 adverse events (SAEs) will be listed.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version MAR21B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by parameter and part, 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.

9.4.4 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 part.

Values for individual participants will be listed.

9.4.5 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.

9.4.6 Product Acceptability and Palatability Assessments

Participants in Part 1 will be asked to provide responses to questions designed to assess the acceptability and palatability of the solution after treatment administration. The questionnaire will assess the participant's experience relating to the taste, mouthfeel, and aftertaste of the solution in the oral cavity. The questionnaire will be completed by the participant immediately after administration of the solution i.e. within 5 minutes of dosing.

These data will be summarized by part, and listed.

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, 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 AL T≥2× baseline, AST ≥2× baseline, AL P≥2× baseline, or TBL ≥1.5× baseline.

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, 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 ≥3× 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 ≥2× 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 an SAE

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 Other assessments

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

9.4.9 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned.

10. INTERIM ANALYSES

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol and SAP must be amended.

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

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