Statistical Analysis Plan: J2N-MC-JZNW (Final Version 1.0)

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single and Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

NCT05176314

Approval Date: 22-Dec-2021

STATISTICAL ANALYSIS PLAN

A Phase 1, Open-Label, Drug Interaction Study to Investigate the Effect of Single and Multiple Doses of Pirtobrutinib on the Pharmacokinetics of Rosuvastatin in Healthy Participants

Statistical Analysis Plan Status: Final
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Study Drug: LY3527727 (Pirtobrutinib)

Sponsor Reference: J2N-MC-JZNW
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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 lower limit of quantitation
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
C_{max}	Maximum observed drug concentration
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
MRE	Magnetic resonance elastography
NA	Not applicable
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
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
V_{ss}/F	Apparent volume of distribution at steady state 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 22 October 2021).

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

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

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

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

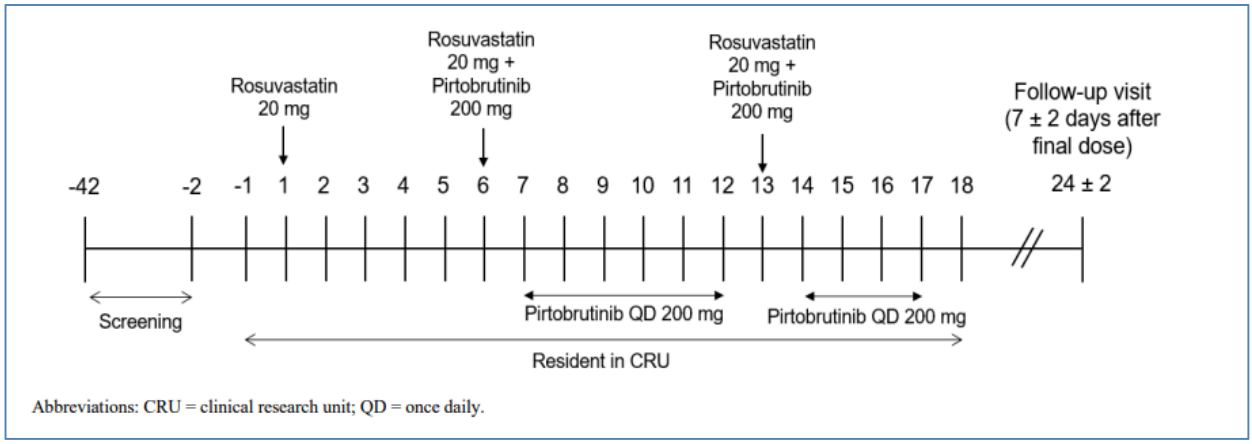
4. STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effect of single and multiple doses of pirtobrutinib on breast cancer resistance protein activity in healthy participants.	• Maximum observed drug concentration (C_{max}), area under the concentration versus time curve from time zero to infinity [AUC (0-∞)] of rosuvastatin.
Secondary	
• To evaluate the safety and tolerability of rosuvastatin in combination with pirtobrutinib in healthy participants.	• Incidence of treatment-emergent adverse events and serious adverse events (SAEs).

5. STUDY DESIGN

Study J2N-MC-JZNW is a Phase 1, fixed sequence, open-label study in healthy participants that will investigate the effect of single and multiple doses of pirtobrutinib on the PK of rosuvastatin.

Schema 1- study design.



Abbreviations: CRU = clinical research unit; QD = once daily.

Approximately 36 participants will be enrolled to ensure that at least 28 evaluable participants complete the study.

Screening

All participants will be screened for study inclusion within 42 days prior to enrollment (Day 1). Screening should not occur less than 14 days prior to enrollment (Day 1), in order to allow sufficient time to receive genotyping results.

Treatment and Assessment Period

Participants will check in to the clinical research unit (CRU) on Day -1 and remain resident until discharge on Day 18. While resident at the CRU, all participants will receive study intervention as follows:

- Day 1: 20 mg rosuvastatin alone
- Day 6: 20 mg rosuvastatin co-administered with 200 mg pirtobrutinib
- Days 7 to 12: Once daily (QD) doses of 200 mg pirtobrutinib alone
- Day 13: 20 mg rosuvastatin co-administered with 200 mg pirtobrutinib
- Days 14 to 17: QD doses of 200 mg pirtobrutinib alone.

The PK blood sampling and safety assessments, including vital signs measurements, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), and adverse event (AE) recording, will be performed.

Participants will be discharged from the CRU on Day 18 following completion of study procedures, provided they are deemed medically fit by the investigator or designee.

Follow-Up

Participants will attend an outpatient follow-up visit 7 (± 2) days after the final dose of study intervention. If participants are not able to attend the CRU for this visit, the CRU should contact the participant via phone call to conduct AE and concomitant medication review.

6. TREATMENTS

The following is the study treatment sequence that will be used as a sub header in the TFLs.

Study Treatment Sequence Name	Treatment order in TFL
20 mg rosuvastatin alone (Day 1) / 20 mg rosuvastatin + 200 mg pirtobrutinib (Day 6) / 200 mg pirtobrutinib QD (Days 7 to 12) / 20 mg rosuvastatin + 200 mg pirtobrutinib (Day 13) / 200 mg pirtobrutinib QD (Days 14 to 17).	1

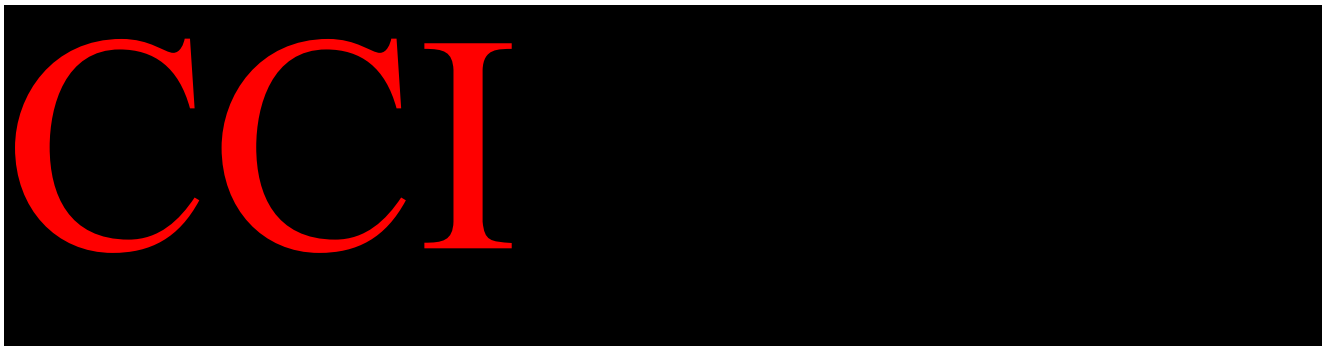
Abbreviation: QD=Once daily.

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

Day	Study Treatment Name	Treatment order in TFL
1	20 mg rosuvastatin	1
6	20 mg rosuvastatin + 200 mg pirtobrutinib	2
7-12	200 mg pirtobrutinib QD	3
13	20 mg rosuvastatin + 200 mg pirtobrutinib	4
14-17	200 mg pirtobrutinib QD	5

Abbreviation: QD=Once daily

7. SAMPLE SIZE JUSTIFICATION



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 study intervention, regardless of whether they take any doses (all enrolled population have meet the inclusion criteria and assigned to study interventions (assigned with planned treatment in DB).

The “Safety” population will consist of all participants who receive at least 1 dose of rosuvastatin. Participants will be analyzed according to the intervention they actually received.

The "Pharmacokinetic" population will consist of all participants who receive at least 1 dose of rosuvastatin and have evaluable PK data.

All protocol deviations and adverse events 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 collected and entered to clinical electronic data base. 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 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 [AUCs] and C_{max}) the geometric mean and geometric CV% will also be presented. For categorical data, frequency count and percentages will be presented. 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 in a given population. 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, 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 for rosuvastatin using non-compartmental procedures in validated software program (Phoenix WinNonlin Version 8.1 or later).

No PK parameters will be derived for the plasma concentrations of pirtobrutinib.

Plasma concentrations of rosuvastatin will be used to determine the following PK parameters, where possible, on Days 1, 6 and 13:

Parameter	Units	Definition
AUC(0-t_{last})	ng.h/mL	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	ng.h/mL	Area under the concentration versus time curve from time zero to infinity
%AUC(t_{last}-∞)	%	Percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	Maximum observed drug concentration
t_{max}	h	Time of maximum observed drug concentration
$t_{1/2}$	h	Half-life associated with the terminal rate constant (λ_Z) in non-compartmental analysis
CL/F	L/h	Apparent total body clearance of drug calculated after extra-vascular administration
V_Z/F	L	Apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}/F	L	Apparent volume of distribution at steady state after extra vascular administration

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 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.

- The 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}.

- 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}.

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

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

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

- The parameters based on the last observed quantifiable drug concentration will be reported.

Individual PK Parameter Rules

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

    - The compound is non-endogenous.

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

    - The time points occur before the first quantifiable concentration.

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

- Also, where two or more consecutive concentrations are BQL towards the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times on the same figure.

- 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 which are greater than ± 10% of the planned sampling time will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the 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 at actual sampling times which are within ± 10% of the planned sampling time. An average concentration estimated with less than 2/3 but more than 3 data points with quantifiable measurements that are within the sampling time as stated above may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the CSR.

Treatment of Outliers during PK Analysis

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

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 $n\geq6$, 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 a typical 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 CSR. Approval of the CSR will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

The PK parameters will be evaluated to estimate drug interaction for rosuvastatin with single (Day 6) and multiple (Day 13) doses of pirtobrutinib compared to rosuvastatin administered alone on Day 1. A participant may be excluded from the PK summary statistics and statistical analysis if the participant has an AE of vomiting that occurs at or before 2 times median t_{max}.

Log-transformed C_{max} and AUC(0-∞) parameters for rosuvastatin will be evaluated in a linear mixed-effects model with a fixed effect for treatment, and a random effect for participant. Treatment can be rosuvastatin with single or multiple doses of pirtobrutinib, or rosuvastatin administered alone.

The least squares (LS) means for each treatment, the difference between the treatment LS means of

- 20 mg rosuvastatin + 200 mg pirtobrutinib on Day 6 (test) – 20 mg rosuvastatin on Day 1(reference)
- 20 mg rosuvastatin + 200 mg pirtobrutinib on Day 13 (test) – 20 mg rosuvastatin on Day 1 (reference)]

associated 90% CIs will be estimated from the model and back-transformed from the log scale to provide estimates of the geometric means, geometric mean ratio, and corresponding 90% CIs.

Example of the SAS code for the analysis:

The t_{max} will be analyzed non-parametrically using a Wilcoxon signed rank test. Estimates of the median difference comparing

- 20 mg rosuvastatin + 200 mg pirtobrutinib on Day 6 (test) – 20 mg rosuvastatin on Day 1 (reference)
- 20 mg rosuvastatin + 200 mg pirtobrutinib on Day 13 (test) – 20 mg rosuvastatin on Day 1 (reference),

corresponding 90% confidence intervals, and p-values from the Wilcoxon signed rank test will be calculated.

Example SAS code to be used for the Wilcoxon signed-rank test:

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-TEAE is defined as an AE which starts after informed consent but prior to dosing. A TEAE 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. TEAEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of participants experiencing an AE and the percentage of participants experiencing an AE) of TEAEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 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.

Discontinuations due to AEs will be listed.

9.4.2 Concomitant medication

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

9.4.3 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.

9.4.4 Vital signs

Vital signs data will be summarized by timepoint together with changes from baseline, where baseline is defined as the Day 1 predose assessment. Figures of mean vital signs and mean changes from baseline profiles will be presented by timepoint.

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 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 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, other substance abuse and additional laboratory tests and/or abdominal imaging studies, as medically indicated.

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

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

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio, viral hepatitis A, B, C, 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 serum TBL to ≥2× ULN (if baseline TBL <1.5× ULN) (except for cases of known Gilbert's syndrome)
   - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2x baseline

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

4. Hepatic event considered to be 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.

9.4.7 Other assessments

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

9.4.8 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 = f4548492-04f8-4913-aaed-4860e39990c2

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