Statistical Analysis Plan H8H-MC-LAIA

Bioequivalence of Lasmiditan Oral Disintegrating Tablet Compared to Current Immediate-Release Tablet Formulation to Support Treatment of Migraine

NCT04881747

Approval Date: 10-Mar-2021

STATISTICAL ANALYSIS PLAN

Bioequivalence of Lasmiditan Oral Disintegrating Tablet Compared to Current Immediate-Release Tablet Formulation to Support Treatment of Migraine

Statistical Analysis Plan Status: Final v1
Statistical Analysis Plan Date: 08-March-2021

Study Drug: Lasmiditan (LY573144)

Sponsor Reference: H8H-MC-LAIA
Covance CRU Study: 1000071-8447232

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
C_{max}	Maximum observed drug concentration
CL/F	Apparent total body clearance of drug calculated after extra vascular administration (not M8)
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
IR	Immediate release
LS	Least square
M8	Metabolite 8
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
OD	Oral disintegrating
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
TBL	Total bilirubin

TEAE	Treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
$t_{1/2}$	Half-life associated with the terminal rate constant (λz) in non-compartmental analysis
t_{max}	Time of maximum observed drug concentration
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state after extra-vascular administration (not M8)
V_z/F	Apparent volume of distribution during the terminal phase after extra-vascular administration (not M8)
WHO	World Health Organization

3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 08 September 2020).

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

4.1 Primary Objective and Endpoint

The primary objective of the study is to evaluate the PK of lasmiditan following administration of a single 100-mg dose of lasmiditan oral disintegrating (OD) tablet (test) administered without water versus the current immediate release (IR) tablet formulation (reference) in healthy participants.

The primary endpoints of the study are:

- Maximum observed drug concentration (C_{max})
- Area under the concentration versus time curve from time zero to infinity [AUC(0-∞)]
- 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-t_{last})]

4.2 Secondary Objectives and Endpoints

The secondary objectives and endpoints of the study are:

- To evaluate the PK of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) administered with water versus the current IR tablet formulation (reference) in healthy participants
    - C_{max}
    - AUC(0-∞)
    - AUC(0-t_{last})
- To evaluate the safety and tolerability of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) versus the current IR tablet formulation (reference) in healthy participants
    - Incidence of treatment-emergent adverse event (TEAEs) and serious adverse events (SAEs)

4.3 Exploratory Objectives and Endpoints

The exploratory objectives and endpoints of the study are:

- To characterize the PK of metabolite 8 (M8) following administration of a single 100-mg dose of lasmiditan OD tablet (test) or the current IR tablet formulation (reference) in healthy participants
    - C_{max}
    - AUC(0-∞)
    - AUC(0-t_{last})
- To assess the product acceptability and palatability of lasmiditan OD tablets
    - Responses to OD tablet acceptability and palatability questionnaire

5. STUDY DESIGN

This study is a Phase 1, open-label, randomized, single-dose, 3-way crossover study in healthy participants. Approximately 48 participants will be enrolled such that 36 participants, 6 per treatment sequence, complete the study.

Screening

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

Treatment and Assessment Period

Eligible participants will take part in 3 separate dosing periods. In each period, participants will be admitted to the clinical research unit (CRU) on Day -1 and remain resident in the CRU until discharge on Day 6. At the discretion of the investigator, participants may remain resident in the CRU for the entirety of the study, i.e., from admission to the CRU on Day -1 of Period 1 until discharge from the CRU on Day 6 of Period 3, after all assessments have been completed.

There will be a washout period of ≥5 days between the day of dosing in 1 period and the day of dosing in the subsequent period. Days 5 and 6 of Period 1 and 2 may coincide with Days -1 and 1 of Period 2 and 3, respectively, provided the required washout between lasmiditan doses is observed.

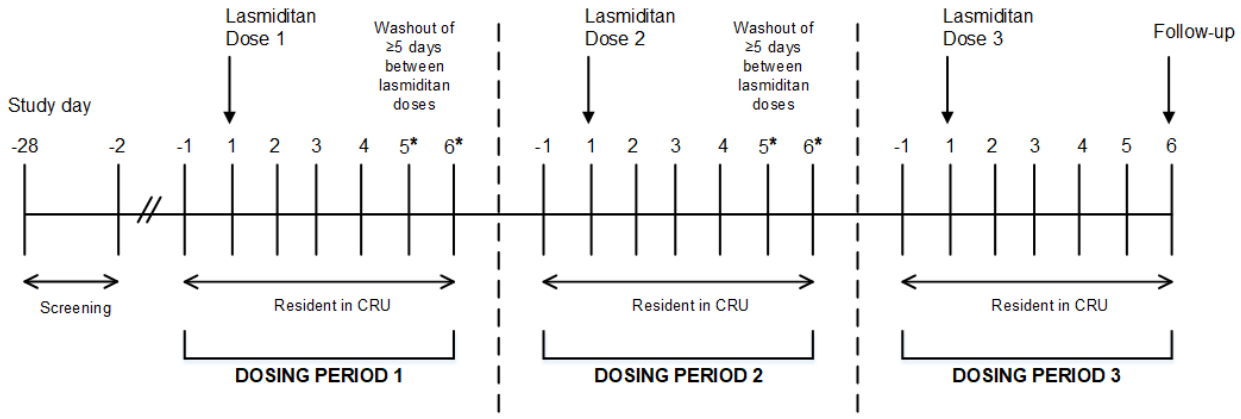
On Day 1 of Period 1, participants will be equally randomized to receive a 100-mg oral dose in 1 of 6 dosing sequences in each of 3 dosing periods.

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

Follow-up

Day 6 of Period 3 will be considered the final visit of the study.

A general schema for this study can be seen in Figure 1.



* Days 5 and 6 may be equivalent to Days -1 and 1, respectively, for the next treatment period if a minimum of 5 days between lasmiditan doses is observed

Figure 1: H8H-MC-LAIA Study Schema

6. TREATMENTS

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

Sequence	Study Treatment Sequence*	Treatment order in TFL
1	100 mg Lasmiditan IR (reference) / 100 mg Lasmiditan OD without water (test) / 100 mg Lasmiditan OD with water (test)	1
2	100 mg Lasmiditan IR (reference) / 100 mg Lasmiditan OD with water (test) / 100 mg Lasmiditan OD without water (test)	2
3	100 mg Lasmiditan OD without water (test) / 100 mg Lasmiditan OD with water (test) / 100 mg Lasmiditan IR (reference)	3
4	100 mg Lasmiditan OD without water (test) / 100 mg Lasmiditan IR (reference) / 100 mg Lasmiditan OD with water (test)	4
5	100 mg Lasmiditan OD with water (test) / 100 mg Lasmiditan IR (reference) / 100 mg Lasmiditan OD without water (test)	5
6	100 mg Lasmiditan OD with water (test) / 100 mg Lasmiditan OD without water (test) / 100 mg Lasmiditan IR (reference)	6

*Abbreviations: IR = immediate release; OD = oral disintegrating

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

Study Treatment Name*	Treatment order in TFL
100 mg lasmiditan IR (reference)	1
100 mg lasmiditan OD without water (test)	2
100 mg lasmiditan OD with water (test)	3

*Abbreviations: IR = immediate release; OD = oral disintegrating

7. SAMPLE SIZE JUSTIFICATION

A total of 36 participants are required to complete the study to establish equivalence between the OD tablet formulation without water and the current IR tablet, based on the PK parameters measured.

Given the 6×3 design, this would mean at least 6 participants would be randomly assigned to each of the 6 dosing sequences. The calculated total number of participants assumes 90% power for the two one-sided test for equivalence with a significance level of 5%, analogous to a 90% confidence interval. Further, this is based on:

- a nominally assigned true mean ratio of 1.05
- a coefficient of variation for C_{max} of 24.1%
- ratio testing boundaries of 0.8 and 1.25

Assuming that 25% of participants will drop out or fail to provide full study data, approximately 48 participants should be enrolled to ensure that 36 participants, 6 per treatment sequence, will complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The “Enrolled” population will consist of all participants randomly assigned to lasmiditan.

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

The "Pharmacokinetic" population will consist of all enrolled participants who received at least 1 dose of lasmiditan and have evaluable PK data. Participants may be excluded from the PK summary statistics and statistical analysis if a participant has an adverse event of vomiting that occurs at or before 2 times median time of maximum observed drug concentration (t_{max}).

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, min, max 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 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, Baseline Characteristics, and Participant Disposition

Participant disposition will be summarized and listed. The demographic and baseline characteristics 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

Noncompartmental methods applied with a validated software program (WinNonlin Phoenix v8.1 or later) to the plasma concentrations of LY573144 and its metabolite M8 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-t_{last})	ng*h/mL	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	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 (not M8)
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (not M8)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration (not M8)

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.

- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one timepoint, t_{max} will be assigned to the first occurrence of C_{max}.

- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the LLOQ, with at least one of these concentrations following C_{max}. 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 associated with the terminal rate constant (λz) in non-compartmental analysis ($t_{1/2}$) 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 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.

    - Predose concentrations > 5% C_{max} will be flagged with exclusions to be noted.

    - The time points occur before the first quantifiable concentration.

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

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

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.

- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.

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

- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.

- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.

- Concentrations excluded from the mean calculation will be documented in the CSR.

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

9.3.2 Pharmacokinetic Statistical Methodology

Log-transformed AUC (0-∞), AUC(0-t_{last}), and C_{max} of lasmiditan will be evaluated in a linear mixed-effects model[3] with fixed effects for period, sequence, and treatment and a random effect for participant within sequence.

Example SAS Code:

```
proc mixed data = xxx;
  by parameter;
  class treatment period sequence participant;
  model log_pk = treatment period sequence / cl residual;
  random participant(sequence);
  lsmeans treatment / cl pdiff alpha = 0.1;
  ods output lsmeans=lsmeans diffs=diffs;
run;
```

All valid PK data will be included, whether or not the participants completed all 3 periods.

Estimates of geometric least square (LS) mean ratios together with the corresponding 90% CIs will be derived for the comparisons of AUC (0-∞), AUC(0-t_{last}), and C_{max} as follows:

- Primary endpoint: lasmiditan OD tablet without water (test) versus lasmiditan IR tablet
- Secondary endpoint: lasmiditan OD tablet with water (test) versus lasmiditan IR tablet.

The 2 lasmiditan formulations will be considered bioequivalent if the 90% CIs of the ratio of geometric LS means of AUC (0-∞), AUC(0-t_{last}), and C_{max} falls completely within 0.80 to 1.25.

Values of t_{max} will be analyzed non-parametrically using the Wilcoxon signed rank[4] test. Estimates of the median difference between test and reference formulations based on the observed medians, 90% CIs, and the p-value from the Wilcoxon test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

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 the first dose. 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 23.0 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 SAEs 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 MAR20B3). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry, hematology, and 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 within each period. Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment.

Values for individual participants will be listed.

9.4.5 Electrocardiogram

All 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 Analyses

Participants will be asked to provide responses to questions designed to assess the acceptability and palatability of the OD tablet when administered with and without water. The questionnaire will be completed by the participant immediately after administration of the OD tablet both with and without water, and will assess the participants' experience relating to the taste, smell, mouthfeel, aftertaste, and the approximate disintegration time of the OD tablet in the oral cavity.

Responses from the product acceptability and palatability questionnaire will be summarized categorically (frequency and percentage) by treatment, 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 ALT≥2× baseline, AST≥2× baseline, ALP≥2× baseline, or TBL≥2× 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≥1.5× 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≥3x baseline on 2 or more consecutive tests

2. Elevation of TBL to ≥2× ULN (if baseline TBL <1.5× ULN)
   - In participants with baseline TBL ≥1.5× ULN, the threshold should be TBL ≥2x baseline

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 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.

3. Brown H, Prescott R. *Applied Mixed Models in Medicine*. Chichester: John Wiley & Sons, 1999.

4. Lehmann EL. *Nonparametrics: Statistical Methods Based on Ranks*. San Francisco, CA: Holden-Day; 1975.

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.”

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