Statistical Analysis Plan H8H-MC-LAHA

Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects

NCT03182920

Approval Date: 05-Jul-2017

STATISTICAL ANALYSIS PLAN

Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 03-July-2017

Study Drug: LY573144 (Lasmiditan)

Sponsor Reference: H8H-MC-LAHA
Covance CRU Study: 1000071-8364953

Clinical Phase I

Approval Date: 05-Jul-2017 GMT

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	Area under the concentration versus time curve from zero to infinity
AUC(0-tlast)	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(tlast-∞)	Percentage of AUC(0-∞) extrapolated
BMI	Body mass index
BQL	Below the level of quantitation
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CSR	Clinical Study Report
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
GGT	Gamma-glutamyl transferase
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
MRE	Magnetic resonance elastography

MW	Molecular weight
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
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_{ss}/F	Apparent volume of distribution during the terminal phase after extra-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 27 April 2017).

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 between Eli Lilly and Company and Covance Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be signed off prior to first subject administration 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 between Eli Lilly and Company and Covance EC Biometrics 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 Council 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

4.1 Primary objective

- To determine the PK of lasmiditan in healthy elderly subjects (≥65 years of age) following a single 200 mg oral dose of lasmiditan.

4.2 Secondary objectives

- To compare the PK of lasmiditan in healthy elderly subjects (≥65 years of age) against the PK of lasmiditan in healthy young subjects (18 to 45 years of age) following a single 200 mg oral dose of lasmiditan.
- To assess the safety and tolerability of a single 200 mg oral dose of lasmiditan in elderly and young healthy subjects.

4.3 Exploratory objective

- To determine the PK of the metabolites M8, M7, and M18 in healthy elderly and young subjects following a single 200 mg oral dose of lasmiditan.

5. STUDY DESIGN

This is a single dose study to determine the PK of lasmiditan following a single 200 mg oral dose in healthy elderly and young subjects. Two groups of subjects will be evaluated as follows:

- Group 1 (healthy elderly subjects; ≥65 years): 200 mg lasmiditan and placebo in a randomized, double-blind, 2-period crossover design.
- Group 2 (healthy young subjects; 18 to 45 years, inclusive): 200 mg lasmiditan in an open label design.

Subjects in Group 2 will be matched by primary race, sex, and body mass index (BMI) (±20%) to subjects in Group 1 where feasible. Both groups may be studied concurrently.

Screening Period:
All subjects will participate in a screening visit up to 28 days prior to study drug dosing.

Dosing Period:
Subjects in Group 1 will participate in 2 dosing periods. They will be admitted to the clinical research unit (CRU) on the day prior to dosing (Day -1), and receive study drug on Day 1 for each dosing period. Subjects may be discharged from the CRU on Day 3 based on investigator discretion. There will be a washout period of 3 to 10 days between each dose. Subjects may stay in the CRU as inpatient during the entire dosing period.

Subjects in Group 2 will participate in 1 dosing period. They will be admitted to the CRU on Day -1 and receive study drug on Day 1. Subjects may be discharged from the CRU on Day 3 based on investigator discretion.

All subjects will be discharged from the study approximately 7 days post their final dose of lasmiditan.

6. TREATMENT

The following is a list of the study treatments and age group names that will be used in the TFLs.

Treatment Name	Order in TFL
Placebo	1
200 mg lasmiditan	2

Age Group Name	Order in TFL
Elderly	1
Young	2

7. SAMPLE SIZE JUSTIFICATION

Up to 36 subjects may be enrolled in order that 30 subjects (2 groups of 15) complete the study. For area under the curve (AUC) or maximum observed drug concentration (C_{max}), assuming inter-subject coefficient of variation (CV) of 40% and a sample size of 15 per group, the 90% confidence interval around the ratio of the geometric means (elderly group : non-elderly group) will have half-width of 24.3% on the log scale with 90% coverage probability.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of study drug or placebo, and have at least one postdose safety assessment.

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of study drug and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject 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 subjects 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: AUCs and C_{max}) the geometric mean and geometric CV% will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects 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 subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject'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 9.3 or greater.

9.2 Demographics and Subject Disposition

Subject 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.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

Plasma concentrations of lasmiditan (LY573144) and its metabolites M8, M7 and M18 will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from zero to infinity
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(t_{last}-∞)	%	percentage of AUC(0-∞) extrapolated
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
$t_{½}$	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 (LY573144 only)
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (LY573144 only)
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration (LY573144 only)
MR		metabolic ratio[a]

[a] = no molar correction will be applied since the metabolites are very similar in molecular weight and within 5% of the molecular weight for lasmiditan.

Additional PK parameters may be calculated, as appropriate. The software and version used for the final analyses will be specified in the clinical study report. Any exceptions or special handling of data will be clearly documented within the final study report.

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.
- C_{max} and t_{max} will be reported from observed values. If C_{max} occurs at more than one time point, t_{max} will be assigned to the first occurrence of C_{max}.
- AUC parameters will be calculated using a combination of the linear and logarithmic trapezoidal methods (linear-log trapezoidal rule). The linear trapezoidal method will be applied up to t_{max} and then the logarithmic trapezoidal method will be used after t_{max}. The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}. $AUC_{(0-\infty)}$ 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 ($t_{½}$) 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 subject 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 $t_{½}$ is estimated over a time window of less than 2 half-lives, the values will be flagged in the data listings. Any $t_{½}$ 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 concentration at last quantifiable timepoint (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 subject or from a subsequent dose period following a suitable wash-out period.
    - The time points occur before the first quantifiable concentration.
- All other BQL concentrations that do not meet the above criteria will be set to missing.

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

Individual Concentration vs. Time Profiles

- Individual concentrations will be plotted utilizing actual sampling times.
- The terminal point selections will be indicated on a semi-logarithmic plot.

Average Concentration vs. Time Profiles

- The average concentration profiles will be graphed using scheduled (nominal) sampling times.
- The average concentration profiles will be graphed using arithmetic average concentrations.
- The pre-dose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all pharmacokinetic 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.

<u>Data Within an Individual Profile</u>
A value within an individual profile may be excluded from analysis if any of the following criteria are met:

- For pharmacokinetic 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 pharmacokinetic profiles during single dosing of non-endogenous compounds, the concentration in a pre-dose sample is quantifiable.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data Between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.
2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:
    a. Transform all values in the calculation to the logarithmic domain.
    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.
    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.
    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.
    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and n ≥ 6 following the exclusion, then repeat step 2 above. This evaluation may be repeated as many times as necessary, excluding only one suspected outlier in each iteration, until all data remaining in the dataset fall within the range of arithmetic mean ±3*SD of the log-transformed values.

Reporting of Excluded Values
Individual values excluded as outliers will be documented in the final report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

The PK parameter estimates will be evaluated to determine the impact of age on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC(0-∞) will be evaluated in a linear fixed-effects model with a fixed effect of age group (elderly, young). The 90% confidence intervals (CIs) of the ratios of geometric means of the elderly group versus the young group will be presented. An example of the SAS code that will be used is as follows:

```
proc mixed data=xxx;
class agegroup;
model l_pk = agegroup / alpha=0.1;
lsmeans agegroup / pdiff;
run;
```

where l_pk is the log-transformed (base e) PK parameter.

The t_{max} will be analyzed using a Wilcoxon rank sum test. Estimates of the median difference between elderly and young subjects based on the observed medians, 90% CIs and the p-value from the Wilcoxon test will be calculated.

Additional analysis will be performed if warranted upon review of the data.

9.4 Safety and Tolerability Assessments

9.4.1 Adverse events

Where changes in severity are recorded in the Case Report Form (CRF), each separate severity of the adverse event (AE) will be reported in the listings, only the most severe will be used in the summary tables. A pre-existing condition is defined as an AE that starts before the subject 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 age group, treatment, severity and relationship to the study drug. The frequency (the number of adverse events, the number of subjects experiencing an adverse event and the percentage of subjects experiencing an adverse event) of treatment-emergent adverse events will be summarized by age group, treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 system organ class and preferred term. The summary and frequency adverse event tables will be presented for all causalities and those considered related to the study drug. Any serious adverse events will be tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2016 Enhanced Dictionary B2 Format). 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.

Values for any clinical chemistry, hematology and urinalysis values outside the reference ranges will be flagged on the individual subject data listings.

9.4.4 Hepatic Monitoring

If a subject experiences elevated alanine aminotransferase (ALT) $\geq 3 \times$ upper limit of normal (ULN), alkaline phosphatase (ALP) $\geq 2 \times$ ULN, or elevated total bilirubin (TBL) $\geq 2 \times$ ULN, liver tests will be performed to confirm the abnormality.

The subjects' liver disease history and associated person liver disease history data will be listed. Any concomitant medication of acetaminophen/paracetamol will be listed. Results from any

hepatic monitoring procedures, such as a magnetic resonance elastography (MRE) scan and a biopsy assessment will be listed, if performed.

Hepatic risk factor assessment data will be listed. Liver related signs and symptoms data will be summarized by age group and treatment, and listed, if available.

All hepatic chemistry, hematology, coagulation, and serology data will be summarized by parameter, age group, and treatment, and listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.4.5 Vital signs

Where supine (or semi-recumbent for elderly subjects) blood pressure and pulse rate are measured in triplicate, the mean value will be calculated and used in all subsequent calculations. When triplicate blood pressure or pulse rate measurements precede a standing measurement, the last supine (or semi-recumbent for elderly subjects) blood pressure or pulse rate measurement will be used for orthostatic calculations. Orthostatic changes will be calculated as the standing value, minus the last supine (or semi-recumbent for elderly subjects) value taken prior to the standing value.

Vital signs data will be summarized by age group and treatment together with changes from baseline, where baseline is defined as the mean of the triplicate measurement on Day 1 predose of each treatment period for supine (or semi-recumbent for elderly subjects) vital signs, and the last measurement on Day 1 predose of each treatment period for standing and orthostatic vital signs. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by age group and treatment over time. Furthermore, values for individual subjects will be listed.

Changes from baseline will be calculated for vitals signs. Changes from baseline of >30 mmHg for systolic blood pressure and of >20 mmHg for diastolic blood pressure are considered to be of potential clinical concern and will be highlighted on the individual changes from baseline data listings. Orthostatic decreases of >20 mmHg for systolic and diastolic blood pressure or an increase in heart rate of >20 bpm are considered to be of potential clinical concern, and will also be highlighted on the individual data listings.

9.4.6 Electrocardiogram (ECG)

For each subject, ECGs will be performed for safety purposes only, and will not be reported.

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

Since the data will not be paired due to the study design, Wilcoxon rank sum test will be used for the analysis of t_{max} instead of the Wilcoxon signed rank test that was stated in the protocol.

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 subjects or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the centre of the table, such as, “No serious adverse events occurred for this study.”

Leo Document ID = 2263d53e-f038-48e7-ae74-397afc94edbe

Approver: PPD
Approval Date & Time: 05-Jul-2017 12:17:40 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 05-Jul-2017 12:59:09 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 05-Jul-2017 13:02:55 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 05-Jul-2017 13:15:00 GMT
Signature meaning: Approved