Statistical Analysis Plan H8H-MC-LAIC

Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects

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STATISTICAL ANALYSIS PLAN

Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects

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Study Drug: Lasmiditan (LY573144)

Sponsor Reference: H8H-MC-LAIC
Covance CRU Study: 1001215-8390215

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]).

AE	Adverse event
AUC	Area under the concentration versus time curve
AUC_{τ}	Area under the concentration versus time curve during one dosing interval (i.e. 24 h)
$AUC(0\text{-}t_{last})$	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
$AUC(0\text{-}\infty)$	Area under the concentration versus time curve from time zero to infinity
$\%AUC(t_{last}\text{-}\infty)$	Percentage of $AUC(0\text{-}\infty)$ extrapolated
BQL	Below the quantifiable lower limit of the assay
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CRF	Case Report Form
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CRU	Clinical Research Unit
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
IP	Investigational product
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
NA	Not applicable
PK	Pharmacokinetic
R_A	Accumulation ratio (based on C_{max} and AUC_{τ})

RI	linearity ratio between AUCτ after multiple dosing day and AUC(0-∞) after single dosing day
SAP	Statistical Analysis Plan
SD	Standard deviation
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
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 09 August 2018).

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 evaluate the PK of single and multiple doses of lasmiditan in healthy Chinese subjects.

4.2 Secondary objective

To explore the safety and tolerability of single and multiple oral doses of lasmiditan in healthy Chinese subjects.

4.3 Exploratory objective

To evaluate the PK of metabolites M7, M8, (S,R)-M18, and (S,S)-M18 in healthy Chinese subjects

5. STUDY DESIGN

This study is a Phase 1, investigator- and subject-blinded, randomized, placebo-controlled study in healthy Chinese subjects.

Subjects will be enrolled into 1 of 3 cohorts and receive single and multiple doses of lasmiditan or placebo in a parallel design. Each cohort will comprise 12 subjects (10 lasmiditan: 2 placebo) and will be assigned the following doses:

- Cohort 1 = 50 mg lasmiditan (or placebo)
- Cohort 2 = 100 mg lasmiditan (or placebo)
- Cohort 3 = 200 mg lasmiditan (or placebo)

Subjects will be evaluated for study eligibility ≤28 days prior to enrollment. Subjects who fulfil the eligibility criteria will be admitted to the clinical research unit (CRU) on Day -1 (the day before their first dose of lasmiditan or placebo).

After randomization on Day 1, investigational product (IP: lasmiditan or placebo) will be administered orally once on the morning of Day 1 after an overnight fast of at least 8 hours. Following a period of at least 72 hours without IP dosing, subjects will receive multiple once-daily oral doses of IP on Days 4 to 10 (7 days of dosing), after overnight fasts of at least 8 hours prior to each dose. The doses of lasmiditan administered on Days 4 to 10 will be the same dose as that administered on Day 1 for each subject.

Subjects will be discharged from the CRU on Day 12 following completion of all scheduled procedures and will attend a follow-up visit approximately 7 to 10 days following final oral dose of IP.

The planned study duration for each subject will be up to 50 days.

Blood samples will be collected for PK analysis. Safety and tolerability will be assessed throughout the study by means of adverse event (AE) review, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS).

6. TREATMENTS

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

Study Treatment Name	Treatment order in TFL
Placebo	1
50 mg lasmiditan	2
100 mg lasmiditan	3
200 mg lasmiditan	4

7. SAMPLE SIZE JUSTIFICATION

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but not administered treatment may be replaced to ensure that approximately 8 subjects per cohort, who receive lasmiditan, may complete the study.

8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects who received at least 1 dose of IP, whether or not they completed all protocol requirements.

The "Pharmacokinetic" population will consist of all subjects who receive at least one dose of lasmiditan and have evaluable PK.

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.

Placebo subjects will be pooled across cohorts.

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 curves [AUCs] and the maximum observed drug concentration [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 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 9.4 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

Pharmacokinetic (PK) parameter estimates will be determined using non-compartmental procedures in a validated software program (Phoenix WinNonlin Version 6.4 or later).

Plasma concentrations of lasmiditan (LY573144) and its metabolites (M7, M8, [S,R]-M18 and [S,S]-M18) will be used to determine the following PK parameters for single and multiple dose (unless otherwise specified), when possible:

Parameter	Units	Definition
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
AUC_{τ}	ng.h/mL	area under the concentration versus time curve during one dosing interval (i.e. 24 h)
$AUC(0\text{-}t_{last})$	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
$AUC(0\text{-}\infty)$	ng.h/mL	area under the concentration versus time curve from time zero to infinity (after single dose only)
$\%AUC(t_{last}\text{-}\infty)$	%	percentage of $AUC(0\text{-}\infty)$ extrapolated (after single dose only)
$t_{1/2}$	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 (LY573144 only)
V_Z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration (LY573144 only)
R_A		accumulation ratio (based on C_{max} and AUC_{τ}) (after multiple dose only - LY573144 only)
RI		linearity ratio between $AUC\tau$ after multiple dosing day and $AUC(0\text{-}\infty)$ after single dosing day (LY573144 only)
MR		metabolic ratio[a] (after multiple dose only)

[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.

Trough concentrations of lasmiditan and its metabolites will be evaluated graphically and descriptively for achievement of steady-state. No formal analysis will be performed for attainment of steady-state.

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.

- Both C_{max} and time of maximum observed drug concentration (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-∞) 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 predicted 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 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 report. Approval of the final report will connote approval of the exclusion.

9.3.2 Pharmacokinetic Statistical Methodology

All PK parameters will be summarized by analyte and treatment, and listed. Plots of mean (+/- SD) plasma concentrations by analyte and treatment over time will be presented.

Pharmacokinetic parameters for lasmiditan will be evaluated to estimate dose proportionality over the 50 to 200-mg dose range on Day 1 and Day 10 separately and will be presented graphically, as well as in analysis tables. Log-transformed C_{max} and AUC parameters (AUC[0-∞] for Day 1 and AUCτ for Day 10) will be evaluated using a power model (where the log of the dose will be an explanatory variable) to estimate ratios of dose-normalized geometric means and the corresponding 90% confidence intervals (CIs). The estimated ratio between the highest and lowest doses will be used to assess dose proportionality. The intersubject coefficient of variation will be derived.

Example SAS code:

```
proc mixed data=pk01;
  by param pkday;
  title1 j=c "Estimate of slope";
  model log_pk = log_dose / solution residual cl alpha=0.1;
  estimate 'xx mg' intercept 1 log_dose yy / alpha=0.1 cl; /*Log value
  of xx*/
  estimate 'zz mg - xx mg' log_dose pp / alpha=0.1 cl; /*Difference in
  log values of zz and xx*/
  ods output estimates=estims;
  ods output solutionf=doseprop;
run;
```

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 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. Adverse events by day of onset will be presented.

All AEs will be listed. Treatment-emergent AEs will be summarized by treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 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. Any serious AEs will be tabulated.

9.4.2 Concomitant medication

Concomitant medication will be coded using the World Health Organization (WHO) drug dictionary (Version March 2018 Enhanced B2). Concomitant medication will be listed.

9.4.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be listed and summarized by parameter, treatment, and timepoint together with changes from baseline, where baseline is defined as Day 1, predose. 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 Vital signs

Orthostatic vital signs will be calculated as the standing value, minus the last supine value taken prior to the standing value.

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

Furthermore, values for individual subjects will be listed.

9.4.5 Electrocardiogram

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

9.4.6 Columbia Suicide Severity Rating Scale and Lilly Self-Harm Supplement

Data from the C-SSRS questionnaire will be listed for individual subjects.

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 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.”

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