Statistical Analysis Plan H8H-MC-LAHC

An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods

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STATISTICAL ANALYSIS PLAN

An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods

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Study Drug: LY573144 (Lasmiditan)

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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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AUC	Area under the concentration versus time curve
AUC(0-∞)	Are 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
%AUC(tlast-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the lower limit of quantification
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
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio
MRE	Magnetic resonance elastography
NA	Not applicable
PK	Pharmacokinetic

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
ULN	Upper limit of normal
V_{ss}/F	Apparent volume of distribution at steady state 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 08 June 2017) and Protocol Amendment (a) (final version dated 13 July 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 assess the PK of lasmiditan in patients with episodic migraine during an acute migraine attack and during their inter-ictal period.

4.2 Secondary Objectives

- To assess the tolerability of a single dose of lasmiditan in patients with episodic migraine.
- To evaluate and compare the PK characteristics of major lasmiditan metabolites (M3, M7, M8, S,R-M18, and S,S-M18) in patients during an acute migraine attack and during the inter-ictal period.

4.3 Exploratory Objective

- To assess the effect of lasmiditan on exploratory biomarkers.

5. STUDY DESIGN

Study H8H-MC-LAHC is a multi-center, open-label study with 2 study periods to be conducted in patients with episodic migraine. Patients will receive 1 oral dose of lasmiditan during an acute migraine attack (Period 1), and 1 oral dose of lasmiditan during their inter-ictal period (Period 2). There will be a washout period of at least 1 week between doses.

All patients will participate in a screening visit. Eligible patients will be instructed to telephone the study site when they feel the onset of migraine symptoms, to arrange to attend for an immediate inpatient stay. Each patient must be admitted to the study site with continuing migraine symptoms within 28 days of the screening visit. Provided they are still experiencing migraine symptoms, patients will receive a single dose of 200 mg lasmiditan on arrival at the study site; this will be defined as Period 1, Day 1. The first dose of lasmiditan must be administered within 24 hours of onset of migraine symptoms; the time of administration will be defined as time = 0. Patients may be discharged from the study site after the last scheduled Day 2 assessment has been performed (24 hours postdose), at the discretion of the investigator, with subsequent Period 1 assessments performed on an outpatient basis. Patients will then telephone the study site again at the onset of their next migraine attack to arrange for a second inpatient stay, which should be scheduled for as soon as possible after the expected resolution of the migraine attack (ie, the next day or, if the migraine is expected to continue into the next day, the following day). This second visit should occur at least 1 week, and up to 4 weeks (but may be extended beyond 4 weeks if necessary, at the investigator's discretion) after their first lasmiditan dose, and will be defined as Period 2, Day 1. Provided the patient is still in their inter-ictal period (defined as not currently experiencing migraine symptoms) on arrival at the site, they will be readmitted as an inpatient and receive a single dose of 200 mg lasmiditan. Patients may be discharged from the study site after the last scheduled Day 2 assessment is complete, at the discretion of the investigator with subsequent Period 2 assessments performed on an outpatient basis. All patients will return for a follow-up visit 4 to 7 days after their last dose of lasmiditan.

Blood samples will be collected predose and up to 72 hours postdose in each period for the measurement of plasma concentrations of lasmiditan and its 5 major metabolites. Safety assessments performed during the study will include AEs, clinical laboratory evaluations, vital signs measurements, ECGs, and physical examinations.

Study governance considerations are described in detail in Appendix 3 of the protocol.

6. TREATMENT

The treatment administered will be a single oral dose of 200 mg lasmiditan on Day 1 of each treatment period.

Period	Treatment Name	Order in TFLs
Acute migraine attack	200 mg lasmiditan (Period 1)	1
Inter-ictal period	200 mg lasmiditan (Period 2)	2

7. SAMPLE SIZE JUSTIFICATION

Approximately 20 patients may be enrolled to ensure 12 patients with adequate PK data complete the study. Patients who do not complete both periods of the study may be replaced.

For area under the concentration versus time curve (AUC) or maximum observed drug concentration (C_{max}), assuming inter-patient CV% of 40% (based on previous studies) and a sample size of 12, the 90% confidence interval (CI) around the geometric mean of the within-patient ratios (migraine/inter-ictal) will have a half-width of 20.1% 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, 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 pharmacokinetic 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 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 9.3 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. All baseline disease characteristics will also be summarized and listed.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

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

Plasma concentrations of lasmiditan (LY573144) and its 5 major metabolites (M3, M7, M8, S,R-M18, and S,S-M18) will be used to determine the following PK parameters, when possible:

Parameter	Units	Definition
C_{max}	ng/mL	maximum observed drug concentration
t_{max}	h	time of maximum observed drug concentration
AUC(0-∞)	ng.h/mL	area under the concentration versus time curve from time 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
$t_{½}$	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-∞) 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

Pharmacokinetic parameter estimates will be evaluated to determine the impact of changes in gastric motility that may accompany acute migraine attacks on the PK of lasmiditan and its metabolites. All plasma concentration data and derived PK parameters will be summarized by period (i.e., migraine status; lasmiditan administered during a migraine versus lasmiditan administered during the inter-ictal period).

Log-transformed C_{max}, AUC(0-tlast), and AUC(0-∞) parameters will be evaluated in a linear mixed-effects model with a fixed effect for period (ie, migraine status; lasmiditan administered during a migraine versus lasmiditan administered during the inter-ictal period) and a random effect for patient. The treatment period differences will be back transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

An example of the SAS code that will be used is as follows:

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

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

The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% confidence intervals, and the p-value from the Wilcoxon test will be calculated.

Additional analysis may be performed if warranted upon review of the data.Insert stats methodology here.

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 period, 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 period, 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 World Health Organization (WHO) drug dictionary (Version March 2017 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) ≥3× upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2× ULN, or elevated total bilirubin (TBL) ≥2× 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 period 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 subject data listings.

9.4.5 Vital signs

Where supine 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 blood pressure or pulse rate measurement will be used for orthostatic calculations. Orthostatic 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 period together with changes from baseline, where baseline is defined as the mean of the triplicate measurement on Day 1 predose of each period for supine vital signs, and the last measurement on Day 1 predose of each period for standing and orthostatic vital signs. Figures of mean vital signs and mean changes from baseline profiles by period will be presented by period 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 Columbia-Suicide Severity Rating Scale (C-SSRS)

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

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.

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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