Statistical Analysis Plan H8H-JE-LAIE (Version 2)

Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Japanese and Caucasian Subjects

NCT03579940

Approval Date: 30-Aug-2018

# STATISTICAL ANALYSIS PLAN

**Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Japanese and Caucasian Subjects**

Statistical Analysis Plan Status: Final v2
Statistical Analysis Plan Date: 28-August-2018

Study Drug: Lasmiditan (LY573144)

Sponsor Reference: H8H-JE-LAIE
Covance CRU Study: 1000071-8381378

Clinical Phase I

Approval Date: 30-Aug-2018 GMT

## 1. TABLE OF CONTENTS

**1.** TABLE OF CONTENTS ..... 2
**2.** ABBREVIATIONS ..... 3
**3.** INTRODUCTION ..... 5
**4.** STUDY OBJECTIVES ..... 5
4.1 Primary Objective ..... 5
4.2 Secondary Objective ..... 5
4.3 Exploratory Objectives ..... 5
**5.** STUDY DESIGN ..... 6
**6.** TREATMENTS ..... 7
**7.** SAMPLE SIZE JUSTIFICATION ..... 7
**8.** DEFINITION OF ANALYSIS POPULATIONS ..... 7
**9.** STATISTICAL METHODOLOGY ..... 8
9.1 General ..... 8
9.2 Demographics and Subject Disposition ..... 8
9.3 Pharmacokinetic Assessment ..... 8
9.3.1 Pharmacokinetic Analysis ..... 8
9.3.2 Pharmacokinetic Statistical Methodology ..... 12
9.4 Safety and Tolerability Assessments ..... 12
9.4.1 Adverse events ..... 12
9.4.2 Concomitant medication ..... 13
9.4.3 Clinical laboratory parameters ..... 14
9.4.4 Vital signs ..... 14
9.4.5 Electrocardiogram (ECG) ..... 14
9.4.6 Hepatic Monitoring ..... 15
9.4.7 Columbia-Suicide Severity Rating Scale (C-SSRS) ..... 16
9.4.8 Other assessments ..... 16
9.4.9 Safety and Tolerability Statistical Methodology ..... 16
**10.** INTERIM ANALYSES ..... 16
**11.** CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES ..... 16
**12.** REFERENCES ..... 16
**13.** DATA PRESENTATION ..... 17
13.1 Derived Parameters ..... 17
13.2 Missing Data ..... 17
13.3 Insufficient Data for Presentation ..... 17
**14.** REVISION OF CHANGES FROM PREVIOUS SAP VERSIONS ..... 17

## 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-$t_{last}$) | 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-∞) | Area under the concentration versus time curve from time zero to infinity |
| %AUC(tlast-∞) | Percentage of AUC(0-∞) extrapolated |
| BQL | Below the lower limit 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 |
| 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 |
| PK | Pharmacokinetic |
| QTcF | QT interval corrected using Fridericia's formula |

| | |
|---|---|
| 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 ($\lambda_z$) 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 |
| ΔQTcF | changes from baseline in QTcF |

# 3. INTRODUCTION

This SAP has been developed after review of the Clinical Study Protocol (final version dated 16 April 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 explore the safety and tolerability of single and repeated oral doses of lasmiditan in healthy Japanese subjects, and single oral doses of lasmiditan in healthy Caucasian subjects.

## 4.2 Secondary Objective

- To evaluate the PK of lasmiditan in healthy Japanese and Caucasian subjects.

## 4.3 Exploratory Objectives

- To evaluate the PK of metabolites M7, M8, (S,R)-M18, and (S,S)-M18 in healthy Japanese and Caucasian subjects.
- To explore the safety, tolerability, and PK of lasmiditan in female subjects compared to male subjects.

## 5. STUDY DESIGN

This is a randomized, 3-period, subject- and investigator-blind, crossover study in healthy Japanese and Caucasian subjects.

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 in Period 1 (the day before their first dose of lasmiditan or placebo.

Subjects will be enrolled into 1 of 3 cohorts. Within each cohort, subjects will be randomized to a treatment sequence, as indicated in Table 1, Table 2, and Table 3. Randomization will be stratified by sex, such there will be an approximately equal number of male and female subjects in each cohort.

**Table 1. Treatment Sequences for Cohort 1; Japanese Subjects**

| Treatment Sequence | Period 1 | Period 2 | Period 3 |
|---|---|---|---|
| **1** | Placebo | 100 mg lasmiditan | 200 mg lasmiditan |
| **2** | 50 mg lasmiditan | Placebo | 200 mg lasmiditan |
| **3** | 50 mg lasmiditan | 100 mg lasmiditan | Placebo |

**Table 2. Treatment Sequences for Cohort 2; Japanese Subjects**

| Treatment Sequence | Period 1 | Period 2 | Period 3[a] |
|---|---|---|---|
| **1** | Placebo | 400 mg lasmiditan | 2 x 200 mg lasmiditan |
| **2** | 50 mg lasmiditan | Placebo | 2 x 200 mg lasmiditan |
| **3** | 100 mg lasmiditan | 400 mg lasmiditan | 2 x placebo |
| **4** | 200 mg lasmiditan | 400 mg lasmiditan | 2 x 200 mg lasmiditan |

[a] Doses administered 2 hours apart

**Table 3. Treatment Sequences for Cohort 3; Caucasian Subjects**

| Treatment Sequence | Period 1 | Period 2 | Period 3 |
|---|---|---|---|
| **1** | Placebo | 100 mg lasmiditan | 200 mg lasmiditan |
| **2** | 50 mg lasmiditan | Placebo | 200 mg lasmiditan |
| **3** | 50 mg lasmiditan | 100 mg lasmiditan | Placebo |
| **4** | 50 mg lasmiditan | 100 mg lasmiditan | 200 mg lasmiditan |

After randomization on Day 1, investigational medical product will be administered orally on the morning of Day 1 after an overnight fast of at least 8 hours. Blood samples will be collected for PK analysis predose, and for up to 48 hours postdose in each period. There will be a washout period of approximately 72 hours between dose administrations across periods.

Subjects will be discharged from the CRU following completion of all scheduled procedures on Day 3 of Period 3, as defined in the Schedule of Activities (Section 2 in the protocol), and will attend a follow-up visit 7 to 10 days following discharge from the CRU on Day 3 of Period 3.

Safety and tolerability will be assessed throughout the study by means of an adverse event (AE) review, physical examinations, body weight, 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 |
| 2 x Placebo | 2 |
| 50 mg lasmiditan | 3 |
| 100 mg lasmiditan | 4 |
| 200 mg lasmiditan | 5 |
| 400 mg lasmiditan | 6 |
| 2 x 200 mg lasmiditan | 7 |

## 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 14 Japanese and 8 Caucasian subjects (approximately 2 per treatment sequence) may complete the study.

## 8. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all enrolled subjects, whether or not they completed all protocol requirements.

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 are 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 [AUCs] and 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 time point. 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, population (Japanese or Caucasian), ethnicity, country of enrolment, site ID, body weight, height and body mass index will be summarized overall and by population, and listed.

Associated person demographic data for individual subjects will be 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 metabolites (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 ($\lambda_z$) 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.
- $C_{max}$ 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 last predicted quantifiable drug concentration ($C_{last}$) 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.
- 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.

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 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 $n\geq6$, 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 summarised by population, as well as population and sex for each treatment, and listed. Plots of mean (+/- SD) plasma concentrations by population, as well as population and sex for each treatment over time will be presented.

Pharmacokinetic parameters for lasmiditan will be evaluated to determine dose proportionality for Japanese (Cohorts 1 and 2 over the 50 to 400 mg dose range, excluding any data from Period 3 in Cohort 2) and Caucasian subjects (Cohort 3, over the 50 to 200 mg dose range). Log-transformed $C_{max}$ and AUC from time 0 extrapolated to infinity [AUC(0-∞)] will be evaluated using a power model (where the log of the dose will be an explanatory variable and subject will be a random effect) to estimate ratios of dose-normalized geometric means and the corresponding 90% confidence intervals (CIs). The estimated ratio between the highest and lowest doses for each population (Japanese, Caucasian) will be used to assess dose proportionality. The intersubject coefficient of variation (CV) will be derived, and the intrasubject CV will also be derived, as appropriate.

Example SAS code:

```
proc mixed data=pk01;
  by popul param;
  title1 j=c "Estimate of slope";
  class usubjid;
  model log_pk = log_dose / solution residual cl alpha=0.1;
  random usubjid;
  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.

The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. All AEs will be listed.

Treatment-emergent AEs will be summarized by treatment (including overall lasmiditan treatment periods and overall placebo treatment period), severity and relationship to the study drug, in separate outputs, split by population, as well as sex within population. Hence the following summary tables will be created:

- Summary of Treatment-Emergent AE (All Causalities) by Population
- Summary of Treatment-Emergent AE (Related to Study Treatment) by Population
- Summary of Treatment-Emergent AE (All Causalities) by Sex Within Population
- Summary of Treatment-Emergent AE (Related to Study Treatment) by Sex Within Population

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 (including overall lasmiditan treatment periods and overall placebo treatment periods), Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 system organ class and preferred term, and split by population, as well as sex within population, in separate outputs. Any serious AEs will be tabulated. Hence the following frequency tables will be created:

- Frequency of Subjects with Treatment-Emergent AE (All Causalities) by Population
- Frequency of Subjects with Treatment-Emergent AE (Related to Study Treatment) by Population
- Frequency of Subjects with Treatment-Emergent AE (All Causalities) by Sex Within Population
- Frequency of Subjects with Treatment-Emergent AE (Related to Study Treatment) by Sex Within Population

Similar outputs but sorting by preferred term, instead of by system organ class and preferred term, will be created. Hence the following summary tables will be created:

- Summary of Treatment-Emergent AE (All Causalities) by Population and Treatment in Order of Frequency
- Summary of Treatment-Emergent AE (Related to Study Treatment) by Population and Treatment in Order of Frequency
- Summary of Treatment-Emergent AE (All Causalities) by Treatment and Sex Within Population in Order of Frequency
- Summary of Treatment-Emergent AE (Related to Study Treatment) by Treatment and Sex Within Population in Order of Frequency

Subject numbers for all TEAEs will be listed. Pre-existing conditions for individual subjects will also be listed.

### 9.4.2 Concomitant medication

Concomitant medication will be coded using the 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 summarized by population, parameter, and treatment, and listed. 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

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.

Vital signs data will be summarized by treatment in separate outputs for each population (Japanese, Caucasian), as well as for each sex within population, together with changes from baseline.

Baseline is defined as follows:

For supine parameters, baseline is the mean of the average values of the triplicate assessments collected at -1 hour, -0.5 hours, and predose on Period 1. All other time points are considered as post baseline, including predose on Periods 2 and 3.

For standing parameters, baseline is the mean of the assessments collected at -1 hour, -0.5 hours, and predose on Period 1. All other time points are considered as post baseline, including predose on Periods 2 and 3.

For orthostatic parameters, baseline is the mean of -1 hour (standing - last supine), -0.5 hours (standing - last supine), and predose (standing - last supine) assessments on Period 1. The other time points are considered as post baseline, including predose on Periods 2 and 3. Here "last supine" means the last supine value taken prior to the standing value.

Figures of mean vital signs and mean changes from baseline profiles will be presented by treatment over time in separate outputs for each population (Japanese, Caucasian), as well as for each sex within population. Furthermore, values for individual subjects will be listed.

### 9.4.5 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR and QT intervals, QRS duration and heart rate. In addition, QTcF (the QT interval corrected using Fridericia's formula) will be calculated as follows:

$$QTcF = \frac{QT}{\sqrt[3]{\left(60/HR\right)}}$$

The ECG data will be listed and summarized by population and treatment, together with changes from baseline, where baseline is defined as the mean of the average values of the triplicate assessments collected at -1 hour, -0.5 hours, and predose on Period 1. All other time points are considered as post baseline, including predose on Periods 2 and 3.

Figures of mean ECG data and mean changes from baseline will be presented by population and treatment. The frequency of subjects with a maximum increase from baseline in QTcF interval will be summarized by population and treatment according to the following categories: >30 ms and >60 ms. In addition, the frequency of subjects with QTcF postdose values, according to the following categories: >450 ms, >480 ms and >500 ms, will be summarized by population and treatment.

The relationship between concentrations of lasmiditan and changes from baseline QTcF (ΔQTcF) will be explored graphically, using different symbols and colours for each group. The comparisons to be explored are:

- Japanese vs Caucasian
- Japanese (Male vs Female)
- Caucasian (Male vs Female)

A linear mixed-effects model will be fitted with the change from baseline in QTcF (ΔQTcF) as the response, the time-matched concentration as a covariate, population or sex and time-matched concentration-by-population (or sex) as fixed effects for the population or sex analysis respectively, and subject as a random effect. Population and sex will be fitted as binary variables, as appropriate (0=Caucasian, 1=Japanese, 0=Male, 1=Female accordingly). The intercept, slope, and random effect covariance from the model along with their 90% CI will be reported. If the model fails to converge, alternative models will be tested. A scatter plot of ΔQTcF versus the concentrations with the fitted lines will also be plotted. Additional analysis may be performed, if deemed necessary.

Example SAS Code:

```
proc mixed data=ecg alpha=0.1;
  class usubjid effect;
  model chg_qtcf = conc + effect + conc*effect / alpha=0.1 cl solution
  residual ddfm=bw;
  random intercept conc / subject=usubjid type=un s;
run;
```

where effect represents “population” for the comparison of Japanse versus Caucasian, and “sex” for the comparison of males versus females within each population.

### 9.4.6 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.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of ALT to ≥5 × ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2 × ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests

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 population and 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 subject data listings.

### 9.4.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

Data from the C-SSRS questionnaire (suicidal ideation and behavior data, self-harm follow-up questionnaire data) will be listed for individual subjects.

### 9.4.8 Other assessments

Dosing details and body weight for individual subjects will be listed.

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.”

# 14. REVISION OF CHANGES FROM PREVIOUS SAP VERSIONS

Version 2 of the SAP was created to include the following major changes/clarifications:

- Overall: The word “race” (Japanese, Caucasian) was replaced by “population”.
- Section. 9.4.4 Vital Signs: The baseline definition was clarified.
- Section. 9.4.5 Electrocardiogram (ECG): The baseline definition was clarified. Additionally, the example SAS code was updated so that the slope can be different for different effect group.

Leo Document ID = 51376821-27eb-4716-8423-df8b02d43af5

Approver: PPD
Approval Date & Time: 29-Aug-2018 12:28:56 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 29-Aug-2018 13:09:33 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 30-Aug-2018 02:25:24 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 30-Aug-2018 04:33:58 GMT
Signature meaning: Approved