STATISTICAL ANALYSIS PLAN

Multiple-Ascending Dose, Safety, Tolerability, Pharmacokinetic, and Drug-Drug Interaction Study of Lasmiditan

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 18-August-2017

Study Drug: LY573144 (Lasmiditan)

Sponsor Reference: H8H-MC-LAHE
Covance CRU Study: 1000071-8366191

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	Amount of drug excreted
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AR	Accumulation ratio
AUC	Area under the concentration versus time curve
AUC_{τ}	Area under the concentration versus time curve during one dosing interval
$AUC(0\text{-}t_{last})$	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(tlast-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
6-βOHC	6-beta hydroxycortisol
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
PD	Pharmacodynamic
PK	Pharmacokinetic
QD	Once daily
QTcB	QT interval corrected using Bazett's formula
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 (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 29 June 2017 and Protocol Amendment (b) (final version dated 31 August 2017).

This SAP describes the planned analysis of the safety, tolerability, pharmacokinetic (PK) and pharmacodynamic (PD) 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

The primary objective of this study is to explore the safety and tolerability of multiple doses of 200 mg and 400 mg lasmiditan in healthy subjects.

4.2 Secondary objectives

The secondary objectives of this study are:

- To evaluate the PK of multiple doses of lasmiditan and its major metabolites.
- To evaluate the effect of multiple doses of lasmiditan on CYP1A2, CYP2C9, and CYP3A activity.
- To evaluate any potential withdrawal symptoms following once-daily dosing of lasmiditan.

4.3 Exploratory objective

The exploratory objectives of this study are:

- To evaluate concentrations of 6-beta hydroxycortisol (6-βOHC) excreted in urine relative to plasma concentrations of cortisol as an indicator of CYP3A induction before and after treatment with 200 and 400 mg lasmiditan for 7 days.
- To profile urine for lasmiditan metabolites after multiple doses.

5. STUDY DESIGN

This study is a Phase 1, investigator and subject-blinded, randomized, placebo-controlled multiple-ascending dose study to assess the effect of once-daily oral dosing of lasmiditan in 2 cohorts of healthy subjects. Cohort 1 will also assess the effects of lasmiditan and its circulating metabolites upon CYP activity by evaluating effects on the PK of components of a coadministered cocktail of CYP substrate drugs.

All subjects will participate in a screening visit up to 28 days prior to admission to the study.

Subjects in Cohort 1will be admitted to the Clinical Research Unit (CRU) on Day -4, and will receive a dose of the probe drug cocktail (100 mg caffeine, 500 mg tolbutamide and 2 mg midazolam) on Day -3 with serial blood samples taken at the times listed in the Schedule of Activities up to 48 hours postdose for assessment of probe drug PK. Subjects will begin receiving oral doses of 200 mg lasmiditan or placebo (at a ratio of 7:3 lasmiditan: placebo) on Day 1, and will be dosed once per day until Day 7 (inclusive). The probe drug cocktail will be coadministered with lasmiditan on Day 7 and serial blood samples will be taken up to 48 hours post dose for the assessment of probe drug PK. Serial blood samples for lasmiditan will be collected up to 24 hours postdose on Day 1 and Day 7; also, blood samples will be taken predose at Days 3, 4, and 5 to assess the steady-state PK of lasmiditan. Subjects will be discharged from the CRU on Day 9 at the discretion of the investigator.

Subjects in Cohort 2 will be admitted to the CRU on Day -1. Subjects will begin receiving oral doses of 400 mg lasmiditan or placebo on Day 1 (at a ratio of 1:1 lasmiditan to placebo) and will be dosed once per day until Day 7 (inclusive). Subjects will be discharged from the CRU on Day 9 at the discretion of the investigator. Serial blood samples will be taken at times listed in the Schedule of Activities of the protocol up to 24 hours postdose on Days 1 and 7 for the assessment of lasmiditan PK. Blood samples will be taken predose at Days 3, 4, and 5 to assess steady-state PK of lasmiditan. The potential for withdrawal symptoms following multiple dosing of lasmiditan will be assessed by daily completion of a benzodiazepine withdrawal questionnaire (Tyrer et. al 1990) by subjects in both cohorts from Day 2 of lasmiditan or placebo dosing until 14 days following the final dose of lasmiditan or placebo. Whilst resident at the CRU, subjects will complete the questionnaire under supervision of CRU staff. Subjects will be administered the questionnaire via phone by a member of CRU staff each day following discharge from the CRU on Day 9 until the follow-up visit in both cohorts. Additionally, the potential for withdrawal symptoms will be assessed using the physician withdrawal checklist on Day 7 and at follow-up.

Subjects in each cohort will return to the CRU for a follow-up visit 14 days after the final dose of lasmiditan. Subjects will be resident at the CRU for 13 days (Cohort 1) and 10 days (Cohort 2)

respectively. The planned study duration for each subject will to 55 days in Cohort 1, and 52 days in Cohort 2, including screening and follow-up visits.

6. TREATMENTS

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

Cohort	Study Treatment Name	Abbreviation	Treatment order in TFL
1	100 mg caffeine + 500 mg tolbutamide + 2 mg midazolam	Probe drug cocktail	1
	Placebo QD	Placebo QD	2
	200 mg lasmiditan QD	200 mg lasmiditan QD	3
	Placebo + 100 mg caffeine + 500 mg tolbutamide + 2 mg midazolam	Placebo QD + Probe drug cocktail	4
	200 mg lasmiditan +100 mg caffeine + 500 mg tolbutamide + 2 mg midazolam	200 mg lasmiditan QD + Probe drug cocktail	5
2	Placebo QD	Placebo QD	6
	400 mg lasmiditan QD	400 mg lasmiditan QD	7

7. SAMPLE SIZE JUSTIFICATION

7.1 Cohort 1

Up to 40 subjects may be enrolled in Cohort 1 in order that 30 subjects complete the study. Subjects will be randomized at a ratio of 7:3 lasmiditan: placebo in order that 21 completing subjects are exposed to lasmiditan and 9 to placebo. Subjects who do not complete the study for non-drug related reasons may be replaced, and replacement subjects will be assigned the same treatment group as the subject being replaced.

Caffeine

For caffeine area under the concentration versus time curve (AUC) the intrasubject coefficient of variance (CV) was estimated to be 21.0% [3]. Based on this assumption, 21 subjects will provide a precision (i.e. half-width of the 90% confidence interval [CI]) of 0.13 on the log scale, with 90% power, which corresponds to 12.4% on the natural scale. For caffeine the maximum observed drug concentration (C_{max}) the intrasubject CV was estimated to be 23.4% [4]. Based on this assumption, 21 subjects will provide a precision of 0.15 on the log scale, with 90% power, which corresponds to 13.7% on the natural scale.

Midazolam

For midazolam AUC the intrasubject CV was estimated to be 40.0% (derived from LY2484595 study I1V-MC-EIAB). Based on this assumption, 21 subjects will provide a precision of 0.24 on the log scale, with 90% power, which corresponds to 21.7% on the natural scale. For midazolam Cmax the intrasubject CV was estimated to be 38.0% (derived from LY2484595 study I1V-MC-EIAB). Based on this assumption, 21 subjects will provide a precision of 0.23 on the log scale, with 90% power, which corresponds to 20.8% on the natural scale.

Tolbutamide

For tolbutamide AUC the intrasubject CV was estimated to be 39.7% (derived from LY2409021 study I1R-FW-GLBD). Based on this assumption, 21 subjects will provide a precision of 0.24 on the log scale, with 90% power, which corresponds to 21.6% on the natural scale. For tolbutamide C_{max} the intrasubject CV was estimated to be 26.8% (derived from LY2409021 study I1R-FW-GLBD). Based on this assumption, 21 subjects will provide a precision of 0.17 on the log scale, with 90% power, which corresponds to 15.4% on the natural scale.

Benzodiazepine Withdrawal Symptom Questionnaire

For the Benzodiazepine Withdrawal Symptom Questionnaire total scores, assuming a mean of 9 in the lasmiditan group, a mean of 1 in the placebo group, and 7.3 common standard deviation (assumptions based on results in Tyrer et al. 1990[5]), 21 lasmiditan subjects and 9 placebo subjects will provide 85% power to detect a significant difference between lasmiditan and placebo (t-test with 2-sided alpha of 0.10).

7.2 Cohort 2

Up to 30 subjects may be enrolled in Cohort 2 in order that 24 subjects complete the study. Subjects will be randomized at a ratio of 1:1 lasmiditan: placebo. Subjects who do not complete the study for non-drug related reasons may be replaced, and replacement subjects will be assigned the same treatment group as the subject being replaced. For the Benzodiazepine Withdrawal Symptom Questionnaire total scores, assuming a mean of 9 in the lasmiditan group, a mean of 1 in the placebo group, and 7.3 common standard deviation (assumptions based on results in Tyrer et al, 1990), 12 lasmiditan subjects and 12 placebo subjects will provide 83% power to detect a significant difference between lasmiditan and placebo (t-test with 2-sided alpha of 0.10).

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. For drug cocktail PK, the PK population will include all data from all subjects receiving at least one dose of drug cocktail with evaluable PK data, according to the treatment the subjects actually received. For lasmiditan PK, the PK population will include all data from all subjects receiving at least one dose of lasmiditan with 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 study drug concentration (t_{max}).

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of study drug or placebo and have evaluable PD data.

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 (M7, M8 and 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_{τ}	ng.h/mL	area under the concentration versus time curve during one dosing interval
$t_{½}$	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)
R_A		Accumulation ratio based upon AUC_{τ} and C_{max}
MR		metabolic ratio[a]
A_e	mg	amount of drug excreted (LY573144 only)
f_e	%	fraction of dose excreted unchanged (LY573144 only)
CL_R	L/h	renal clearance (LY573144 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 (predose) plasma concentrations of LY573144 and its metabolites will be listed and summarised.

Plasma concentrations of caffeine, tolbutamide and midazolam 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
V_z/F	L	apparent volume of distribution during the terminal phase after extra-vascular administration
V_{ss}/F	L	apparent volume of distribution at steady state after extra-vascular administration

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 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 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 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 $n\geq6$, 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

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

The PK parameter estimates of cocktail drugs will be evaluated to delineate the effects of drug interaction in Cohort 1 of the study. Midazolam, tolbutamide, and caffeine administered in the absence of lasmiditan will represent the reference treatments and will be analysed separately. Each drug administered with lasmiditan will represent the test treatments and will be analyzed separately. The comparisons made will be the following:

- Lasmiditan + Probe drug cocktail (Day 7 [Test]) vs Probe drug cocktail (Day -3 [Reference]) – Midazolam PK Parameters
- Lasmiditan + Probe drug cocktail (Day 7 [Test]) vs Probe drug cocktail (Day -3 [Reference]) – Tolbutamide PK Parameters
- Lasmiditan + Probe drug cocktail (Day 7 [Test]) vs Probe drug cocktail (Day -3 [Reference]) – Caffeine PK Parameters

For the primary analysis, log-transformed C_{max}, AUC(0-tlast), and AUC(0-∞) estimates of all probe drugs (midazolam, tolbutamide, and caffeine) will be evaluated in a linear mixed-effects analysis of variance model (ANOVA) with a fixed effect for treatment and a random effect for subject. The treatment differences will be back-transformed to present ratios of geometric least squares means and the corresponding 90% CIs.

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

```
proc mixed data=xxx;
by analyte;
class trtmnt subject;
model l_pk = trtmnt / alpha=0.1;
random subject;
lsmeans trtmnt / 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% CI, and p-values from the Wilcoxon test will be calculated.

The 200 mg and 400 mg lasmiditan log-transformed PK parameters C_{max} and AUC_{τ} will be analyzed using an ANOVA model. The model will include treatment as a fixed effect. Least squares mean for each dose level and 90% CIs will be calculated from model. P-values for the treatment comparison will be presented. These values will be back-transformed to give geometric least squares means, a point estimate and 90% CI for the ratio between the two dose levels.

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

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

A benzodiazepine withdrawal symptom questionnaire will be completed by all subjects from Day 2 of lasmiditan or placebo dosing until 14 days following the final dose of lasmiditan or placebo, in both cohorts. The physician withdrawal checklist will be completed predose on Day 7 and follow-up.

9.4.2 Pharmacodynamic Statistical Methodology

Benzodiazepine withdrawal symptom questionnaire scores and physician withdrawal checklist will be listed, and summarized by cohort and treatment. Total score at each time point will be averaged for each treatment in each cohort based upon the available data, and the lasmiditan group will be compared with the placebo group via t-test at each time point within each cohort. Days 7 and 21 are of main interinterest and analysis of other days will be performed if appropriate. An example of the SAS code that will be used is as follows:

```
proc ttest data=xxxx;
by cohort day;
class trtmnt;
var score;
run;
```

where score is the average total score for each cohort, treatment, and time point.

9.5 Exploratory Assessment

9.5.1 Exploratory Analysis

Plasma levels of cortisol and urinary 6-βOHC will be measured on Days 1 and 7 in Cohort 1 and 2. Twenty-four hour urine collections will begin prior to dosing on Days 1 and 7 in Cohort 1 and 2. Levels of plasma cortisol relative to urinary 6-βOHC (mean concentration over 24 hour period) will be calculated for both days in both cohorts.

9.5.2 Exploratory Statistical Methodology

Exploratory parameters may be listed and summarized by cohort and treatment. Additional analysis will be performed if warranted upon review of the data.

9.6 Safety and Tolerability Assessments

9.6.1 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. 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 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 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.

9.6.2 Concomitant medication

Concomitant medication will be coded using the WHO drug dictionary (Version March 2017 Enhanced Dictionary B2 Format). Concomitant medication will be listed.

9.6.3 Clinical laboratory parameters

All clinical chemistry and hematology data will be summarized by 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.

9.6.4 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 a magnetic resonance elastography (MRE) scan and 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, and treatment, and listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.6.5 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 orpulse rate measurement will be used for orthostatic calculations. Orthostatic changes 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 cohort and treatment, together with changes from baseline, where baseline is defined as the mean of the triplicate measurement on Day 1 predose for each treatment for supine vital signs, and the last measurement on Day 1 predose for each treatment for standing and orthostatic vital signs. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by treatment and cohort over time. Furthermore, values for individual subjects will be listed.

Summary statistics for baseline-corrected pulse rates will also be calculated and presented. The corresponding box plots for the pulse rate and baseline-corrected heart rate will be presented as well.

9.6.6 Electrocardiogram (ECG)

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

9.6.7 Columbia-Suicide Severity Rating Scale (C-SSRS) / Self-Harm Supplement

Data from the C-SSRS questionnaire and Self-Harm Supplement will be listed.

9.6.8 Other assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

9.6.9 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.

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3. Blanchard J, Sawers SJ. The absolute bioavailability of caffeine in man. Eur J Clin Pharmacol. 1983;24(1):93-98

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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.”