Statistical Analysis Plan H8H-MC-LAIF(a) A Phase 1, Randomized, Subject- and Investigator-Blink,Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Stimulated Driving Performance in Healthy Volunteers

NCT03459612

Approval date: 22 May 2018

STATISTICAL ANALYSIS PLAN

A Phase I, Randomized, Subject- and Investigator-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Simulated Driving Performance in Healthy Volunteers

Statistical Analysis Plan Status: Final
Statistical Analysis Plan Date: 14-May-2018

Study Drug: LY573144 (Lasmiditan)

Sponsor Reference: H8H-MC-LAIF
Covance CRU Study: 1000071-8381131

Clinical Phase I

Approval Date: 22-May-2018 GMT

1. TABLE OF CONTENTS

2. ABBREVIATIONS

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

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
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(t_{last}-∞)	Percentage of AUC(0-∞) extrapolated
BMI	Body mass index
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
CRC	Cognitive Research Corporation
CRCDS	Cognitive Research Corporation Driving Simulator
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
CV	Coefficient of variation
EC	Early Clinical
ECG	Electrocardiogram
e.g.	For example (Latin: *exempli gratia*)
ICH	International Council on Harmonisation
KSS	Karolinska Sleepiness Scale
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MR	Metabolic ratio

MRE	Magnetic resonance elastography
NA	Not applicable
NI	Noninferiority
PD	Pharmacodynamic
PK	Pharmacokinetic
SAP	Statistical Analysis Plan
SD	Standard deviation
SDC	Symbol Digit Coding
SDLP	Standard deviation of lateral position
TBL	Total bilirubin level
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
VAS	Visual Analog Scale
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 15 February 2018) and Protocol Amendment (a) (final version dated 21 February 2018).

This SAP describes the planned analysis of the safety, tolerability and 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, Cognitive Research Corporation (CRC), 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

Primary Objective

To determine the duration of effect of acute doses of lasmiditan 100 mg and 200 mg compared to placebo on simulated driving performance in healthy subjects.

Secondary Objectives

- To determine the effects of lasmiditan 100 mg and 200 mg compared to placebo on:
    - self-reported endpoints
    - performance endpoints, and
    - driving performance endpoints
- To evaluate the PK of lasmiditan in healthy subjects following a single 100 mg or 200 mg oral dose of lasmiditan.

Exploratory Objectives

- To determine the effect of acute doses of lasmiditan 100 mg and 200 mg at 8, 12, and 24 hours compared with positive control (diphenhydramine 50 mg) at time of maximum observed drug concentration (t_{max})
- To determine the effects of lasmiditan 100 mg and 200 mg compared with positive control (diphenhydramine 50 mg) on:
  - self-reported endpoints,
  - performance endpoints, and
  - driving performance endpoints
- To evaluate the PK of diphenhydramine
- To evaluate the PK of lasmiditan metabolites M8, M7, M18(S,R), and M18(S,S)

5. STUDY DESIGN

This study is a multicenter, randomized, subject- and investigator-blind, active- and placebo-controlled Williams square design with 4-period (full) crossover using single 100 mg and 200 mg doses of lasmiditan (Figure LAIF.1). Subjects will be randomized to treatment sequences and should complete all 4 periods within that treatment sequence.

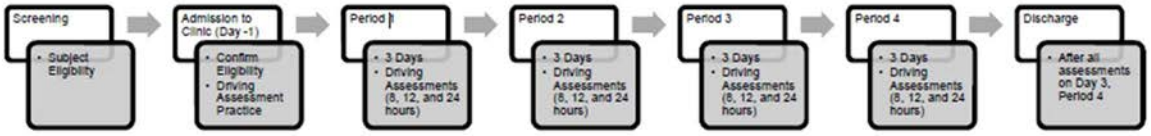

Figure LAIF.1. Study schematic.

Each period will be of 3 days duration, and the minimum washout between periods is 3 days.

Screening (Visit 1) will include procedures to access subject eligibility including clinical laboratory tests, physical examination, and driving simulation training/screening. Prior to randomization, subjects will be screened for simulator sickness and will receive standardized training on the driving simulator and cognitive test battery. Screening procedures and screening assessments may be performed on different days but must be completed within 28 days before Period 1 (Visit 2). The training drives on the driving simulator must be completed no more than 21 days prior to the first dose of study drug. Study drug or placebo will be administered by site staff during each period at 0 (Dose 1), 6 (Dose 2), and 10 (Dose 3) hours on Day 1 and at 22 hours (Dose 4) on Day 2 according to the treatment sequence assigned (Figure LAIF.2). Subjects will wear a blindfold when taking each dose to maintain the blind. The tablet size and shape are deemed similar enough to maintain the blind provided the subject is blindfolded. Driving assessments commence at 8, 12, and 24 hours after Dose 1. The positive control (diphenhydramine 50 mg) is included to establish the sensitivity of the study endpoints.

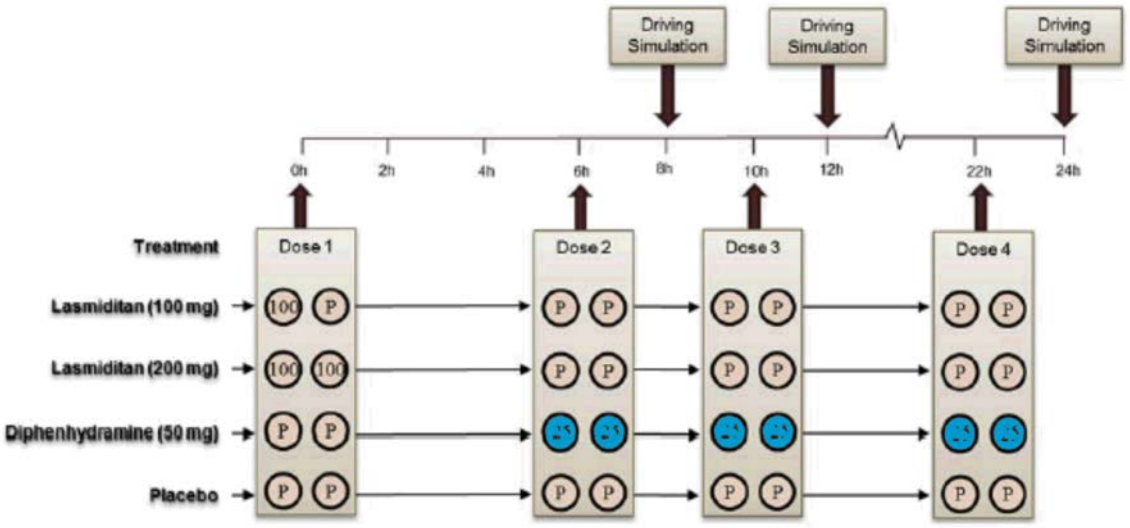

Figure LAIF.2. Timing of doses.

Subjects will be assigned and dosed with study medication (lasmiditan, diphenhydramine, or placebo) according to the treatment sequence they are randomized to. Subjects will be randomized equally into 1 of 4 treatment sequences:

Treatment sequence	Period 1	Period 2	Period 3	Period 4
1	Placebo	Lasmiditan 100 mg	Diphenhydramine 50 mg	Lasmiditan 200 mg
2	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo	Diphenhydramine 50 mg
3	Lasmiditan 200 mg	Diphenhydramine 50 mg	Lasmiditan 100 mg	Placebo
4	Diphenhydramine 50 mg	Placebo	Lasmiditan 200 mg	Lasmiditan 100 mg

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
100 mg Lasmiditan	2
200 mg Lasmiditan	3
50 mg Diphenhydramine	4

7. SAMPLE SIZE JUSTIFICATION

Approximately 72 subjects will be enrolled so that approximately 60 healthy volunteers complete this study. This study is designed to test noninferiority (NI) of lasmiditan relative to placebo, with a diphenhydramine test versus placebo to confirm the sensitivity of the simulator to detect treatment effects. The following assumptions were made in the sample size computation: (a) standard deviation (SD) of differences between lasmiditan and placebo within subject for standard deviation of lateral position (SDLP) is approximately 9.5 cm; (b) the true difference between lasmiditan doses and placebo is 0; and (c) the NI margin is proposed to be 4.4 cm, which is the effect seen with 0.05% of blood alcohol count. Under these assumptions, a sample of 60 subjects would provide >90% power to establish NI of either dose of lasmiditan compared to placebo in terms of the primary end point, SDLP. This sample size is more than adequate to detect diphenhydramine differences, which are anticipated to exceed the NI margin, from placebo.

Subjects who are randomized but who do not complete all 4 periods during the Treatment Phase may be replaced. Replacement subjects will enter the same treatment sequence as the original subjects to complete all 4 periods.

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 the investigational products and have evaluable PK data. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an adverse event (AE) of vomiting that occurs at or before 2 times median t_{max}.

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of the investigational products and have evaluable PD data. Subjects may be excluded from the PD summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median 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. For continuous data, summary statistics will include the arithmetic mean, arithmetic SD, median, min, max and N; for log-normal data (e.g. the PK parameters: area under the concentration versus time curve [AUCs] and the maximum observed drug concentration [C_{max}]) the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary

statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Mean change from baseline is the mean of all individual subjects' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the timepoint. The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Data analysis will be performed using SAS® Version 9.4 or greater.

9.2 Demographics and Subject Disposition

Subject disposition will be listed. The demographic variables age, sex, race, ethnicity, country of enrolment, site ID, body weight, height, and body mass index (BMI) will 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).

Concentrations for lasmiditan and metabolites based on predose samples evaluated for periods 2, 3, 4 may be used for characterizing PK for the preceding period as an additional timepoint (ie 72 hours)

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 (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.

Plasma concentrations of diphenhydramine will be listed and summarized.

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.

9.3.2 General Pharmacokinetic 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.

9.3.3 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.

9.3.4 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.

9.3.5 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.

9.3.6 Treatment of Outliers during Pharmacokinetic Analysis

Application of this procedure to all PK analyses is not a requirement. Rather, this procedure provides justification for exclusion of data when scientifically appropriate. This procedure describes the methodology for identifying an individual value as an outlier for potential exclusion, but does not require that the value be excluded from analysis. The following methodology will not be used to exclude complete profiles from analysis.

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

- For PK profiles during 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.

9.3.7 Pharmacokinetic Statistical Methodology

The PK parameters of lasmiditan and its metabolites will be listed and summarized using standard descriptive statistics, including estimates of intra-subject variability as appropriate. Arithmetic mean (+/- 1 SD) plasma concentration profiles, as well as individual subject profiles, will be presented graphically by treatment over time.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

The primary endpoint (SDLP) and some of the secondary endpoints (Performance [CogScreen Symbol Digit Coding [SDC] test] and Driving performance endpoints) will be analyzed by CRC, whereas the self-reported secondary endpoints (Karolinska Sleepiness Scale [KSS], Self-Perceived Safety to Drive Question and Visual Analog Scale [VAS] to assess subject's motivation and self-appraisal), will be analyzed by Covance EC Biometrics.

SDLP using the Cognitive Research Corporation Driving Simulator- MiniSim (CRCDS-MiniSim) (reported and analyzed by CRC)

SDLP will be used to assess objective level of driving impairment.

The data will be listed, summarized, and analyzed by treatment as outlined in Section 9.4.2 below.

Self-reported secondary endpoints (reported and analyzed by Covance EC Biometrics)

Karolinska Sleepiness Scale (KSS)

The KSS will be used to assess subjective level of sleepiness. This is a subject self-reported measure of situational sleepiness and provides an assessment of alertness/sleepiness at a particular point in time.

The data will be listed, summarized by treatment in frequency tables, and analyzed as outlined in Section 9.4.2 below.

Self-Perceived Safety to Drive Question

Prior to driving, the subject will be asked a simple question as to whether they feel safe to drive ("Right now do you feel safe to drive?"). Subject will answer "yes" or "no".

The data will be listed, summarized by treatment in frequency tables, and analyzed as outlined in Section 9.4.2 below.

VAS to Assess Subject's Motivation and Self-Appraisal

After completing the driving simulation, subjects will assess their own performance and their level of motivation to perform at their best during the driving simulation. Subjects will respond to 2 questions:

1. How well you think you drove for the last 60 minutes?
2. How motivated did you feel to drive at your best during the last 60 minutes of driving?

Subjects will record their response to each question by writing a vertical line on a 100-mm horizontal, linear visual analog scale, indicating their level of performance (0 = Not Satisfactory to 100 = Satisfactory) and motivation (0 = Not Motivated to 100 = Motivated). Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left.

These data will be listed, summarized by treatment, and analyzed as outlined in Section 9.4.2 below.

Performance secondary endpoints (reported and analyzed by CRC)

CogScreen SDC Test

Number of correct responses, accuracy, and standard deviation of reaction time from the CogScreen SDC test will be used to assess treatment-related changes in cognitive functioning.

The data will be listed, summarized, and analyzed by treatment as outlined in Section 9.4.2 below.

Driving performance secondary endpoints (reported and analyzed by CRC)

Lane Exceedance (including number, maximum and duration), Average Speed, Speed Deviation, Speed Count, Excessive Ay (cornering speed threshold exceeded), Total Collisions, and Divided Attention measures (correct responses, omission errors, commission errors, reaction time, standard deviation of reaction time) will be used to assess objective level of driving impairment.

The data will be listed, summarized, and analyzed by treatment as outlined in Section 9.4.2 below.

9.4.2 Pharmacodynamic Statistical Methodology

The primary endpoint, SDLP, will be analyzed using a mixed repeated measures model with fixed effects for sequence, period, and treatment, with repeated observations for subjects for each of the driving time points. An unstructured covariance structure and Kenward-Roger degrees of freedom will be used. In the event an unstructured covariance structure fails to converge, a variance components covariance structure will be assumed. Separate models will be used for each of the driving time points. In addition to assessments of treatment effect, p-values for significance testing of period and sequence effects will be provided.

All secondary endpoints (excluding total collisions and self-reported readiness) will be analyzed for each of the time points using a mixed repeated measures model similar to the one used for the primary analysis, with sequence, period, and treatment as fixed effects, with repeated observations for subject. Separate models will be used for each of the driving and cognition time points. Lane Exceedance will be log transformed as ln[x+1] prior to analyses.

For the primary and secondary endpoints (excluding total collisions and self-reported readiness), pairwise comparisons of differences in means and the corresponding 95% confidence intervals (CIs) of the differences will be provided at each time point for:

- Lasmiditan 100 mg versus placebo
- Lasmiditan 200 mg versus placebo
- Diphenhydramine 50 mg versus placebo

Example SAS code (mixed model for primary and secondary endpoints, including with data sorted for each endpoint as follows):

```
proc sort data=adxx; by atptn usubjid aperiod; run;

proc mixed data=adxx alpha=0.05;
  by atptn;
  class trtpn aperiod trtseqp usubjid ;
  model aval = aperiod trtpn trtseqp / ddfm=kr;
  repeated / sub=usubjid type=un;
  lsmeans trtpn / cl pdiff alpha=0.05;
  estimate '100 vs. Pbo' trtpn -1 1 0 0 / cl alpha=0.05;
  estimate '200 vs. Pbo' trtpn -1 0 1 0 / cl alpha=0.05;
  estimate 'Dip vs. Pbo' trtpn -1 0 0 1 / cl alpha=0.05;
run;
```

In addition, pair-wise within-subject differences in SDLP greater than 4.4 cm in absolute value (equal to the previously found difference between placebo and 0.05% BAC for the CRCDS) will be compared using McNemar's test. Pair-wise, within subject differences in SDLP will also be tested for symmetry about zero (Laska 2012) using the maximally selected McNemar test).

Summary statistics for raw and change from baseline values will be provided (mean, SD, median, minimum, maximum) for primary and secondary endpoints (excluding total collisions and self-reported readiness) for each time point and treatment group.

Figures will be provided for the within subject difference scores by treatment and time point as both a histogram and scatter plot for SDLP.

Self-reported Readiness to Drive

Pairwise comparisons for readiness to drive will be analyzed using McNemar test.

Example SAS code (Pairwise comparisons for readiness to drive using McNemar test):

```
proc freq data=xxx;
        title "McNemar's test for Paired Samples";
        tables treat1*treat2 /agree expected norow nocol nopercent;
run;
```

Total Collisions

Summary statistics will be provided (mean, SD, median, minimum, maximum) for total number of collisions for each time point and treatment group. Additionally, differences in number of collisions for each pair-wise comparison will be provided with their corresponding Wilcoxon Signed Rank p-value. A bar chart will be provided pooling total number of collisions by 0, 1, 2, or >=3 for all 4 treatment groups.

Additional analysis may be conducted if deemed appropriate.

9.4.3 Adjustments for Multiplicity

To address multiplicity of testing associated with 2 doses of lasmiditan versus placebo at 3 time points for the primary endpoint of SDLP, ascending doses of lasmiditan at descending time points will be interpreted in a sequential manner, starting with the 100-mg dose at 24 hours and proceeding to the 200-mg dose and earlier time points via a graphical multiple comparisons procedure, as given in the following figure (Figure LAIF 3). The value of w, the split of alpha after testing 100 mg at 24 hours, will be set to 0.95 (i.e., propagating 95% of alpha to the 100 mg 12 h end point and 5% of the alpha to the 200 mg 24 h end point, assuming the 100 mg 24 h end point is successful).

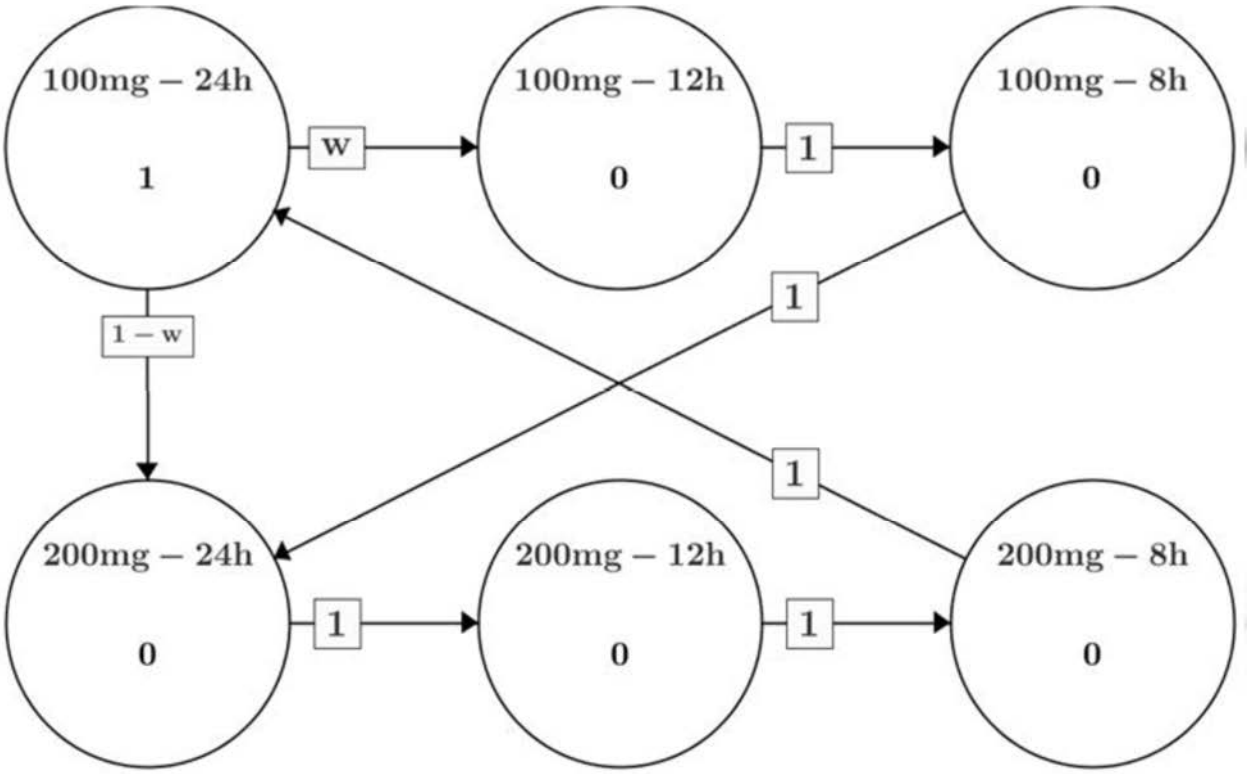

Figure LAIF.3 Pharmacodynamic statistical inference – graphical multiple comparisons procedure.

Doses of lasmiditan will be considered non-inferior to placebo at a time point if the upper 95% CI on the difference in SDLP between that dose and placebo is less than 4.4 cm.

No adjustment to alpha levels will be made for the comparison of diphenhydramine either to placebo or to lasmiditan, or for secondary endpoints or analyses. Strong control of Type I error for non-inferiority, for the primary endpoint will be at the 0.05 alpha-level (two-sided).

9.5 Pharmacokinetic/Pharmacodynamic Assessment

The relationship between the lasmiditan concentrations at 8, 12 and 24 hours (Lasmiditan 100 and 200 mg) and the 8, 12 and 24 hour assessments for SDLP, Lane Exceedance, Speed Deviation, CogScreen SDC number correct, and KSS will be assessed by correlation at each

timepoint separately. Both the Spearman and Pearson correlations will be reported. Tables will provide the correlation coefficient and p-value, which will be provided separately for each treatment group.

For each endpoint of interest, scatterplots including data for both 100 mg and 200 mg will be provided with separate symbols for each dose level.

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 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 treatment, severity and relationship to the study drug. The frequency (the number of AEs, the number of subjects experiencing an AE and the percentage of subjects experiencing an AE) of treatment-emergent AEs will be summarized by treatment, Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated.

9.6.2 Concomitant Medication

Concomitant medication will be coded using the WHO drug dictionary (Version September 2017). 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 Vital Signs

Where two or more repeat measurements are performed for vital signs, the median of the original and the repeat values will be used in all subsequent calculations. Where only one repeat measurement is performed for vital signs, the repeat value will be used in all subsequent calculations.

Vital signs data will be summarized by treatment together with changes from baseline, where baseline is defined as predose of each period.

Furthermore, values for individual subjects will be listed.

9.6.5 Electrocardiogram (ECG)

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

9.6.6 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.

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 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.

9.6.7 Meals

Meal data will be listed for individual subjects.

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

The mixed model specification was updated to use a REPEATED statement rather than a RANDOM statement in the SAS® MIXED procedure, to more readily allow for the estimation of an unstructured covariance matrix. Additional details regarding model specification and outputs are also provided in Section 9.4.2.

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.

3. Laska E, Meisner M, Wanderling J. A maximally selected test of symmetry about zero. Stat Med 2012;31:3178-91.

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.”