H8H-MC-LAHB Statistical Analysis Plan

A Randomized, Subject- and Investigator-Blind, Placebo and Active-Controlled Study to Assess the Abuse Potential of Lasmiditan

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STATISTICAL ANALYSIS PLAN

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Clinical Phase I

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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-∞)	Area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	Area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
%AUC(tlast-∞)	Percentage of AUC(0-∞) extrapolated
BQL	Below the quantifiable lower limit of the assay
C	Control
C_{max}	Maximum observed drug concentration
CI	Confidence interval
CL/F	Apparent total body clearance of drug calculated after extra-vascular administration
CNS	Central nervous system
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*)
E_{max}	Maximal effect score
FDA	Food and Drug Administration
ICH	International Council on Harmonisation
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities

MRE	Magnetic resonance elastography
P	Positive
PD	Pharmacodynamic
PK	Pharmacokinetic
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
VAS	Visual Analog Scale
Vss/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 24 July 2017 and Protocol Amendment (c) (final version dated 06 September 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 Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

4. STUDY OBJECTIVES

4.1 Primary Objective

- To assess the abuse potential of lasmiditan compared to the positive control alprazolam and placebo.

4.2 Secondary Objectives

- Further characterize the abuse potential of lasmiditan with additional Drug Effects and Drug Similarity Visual Analog Scale (VAS) measures
- Safety evaluations
- PK of lasmiditan

4.3 Tertiary/Exploratory Objective

- PK of alprazolam

5. STUDY DESIGN

This study is a Phase 1, randomized, subject- and investigator-blind, placebo- and active-controlled, crossover clinical trial in adult subjects who are recreational poly-drug users. This study includes 4 phases:

Screening Phase: Subjects will sign informed consent before their entry to the study and completion of all screening procedures. Screening visits should be within 28 days of dosing in Qualification Phase. Subjects who fail screening may not be rescreened.

Qualification Phase: Eligible subjects who meet all inclusion criteria and none of the exclusion criteria will enter a subject- and investigator-blind placebo-controlled, 2-period crossover design Qualification Phase. Subjects will be randomized to a test dose of 1 mg alprazolam and placebo in a crossover manner with a washout period of at least 3 days (72 hours) between each dose. "Drug-liking" response will be assessed before and after alprazolam and placebo administration using a 100 mm bipolar Drug Liking VAS. Only subjects who meet alprazolam qualification criteria as detailed below will be eligible to enter the Treatment Phase.

In order to qualify for the Treatment Period of the study, subjects must demonstrate the ability to discriminate an alprazolam test dose from placebo, using the 100 mm bipolar Drug Liking VAS, as defined by:

- Acceptable placebo response ranging from 40 to 60 (inclusive) on the 100 mm bipolar VAS for Drug Liking "at this moment".
- $\geq$ 15 mm increase in "liking" alprazolam more than placebo.
- Subject is able to tolerate the 1 mg dose of alprazolam, as judged by the investigator, including the ability to complete all PD assessments within 4 hours postdose.
- General behavior suggests that the subject could successfully complete the study, as judged by the study site personnel.

On a case-by-case basis, a subject who meets all of the above criteria, with the exception of sporadic erroneous responses, may be permitted into the Treatment Phase, provided that the investigator or designee determines that the subject's response was made in error and that the subject can be successfully retrained regarding proper completion of that assessment.

Treatment Phase: This will be a subject- and investigator-blind, placebo- and active-controlled, 5-period crossover design. Subjects will be randomized to 1 of 10 dosing sequences; each dosing sequence consists of 5 dosing periods that evaluate the abuse potential of 1 of the 5 study treatments: placebo, 2 mg alprazolam, and 100 mg lasmiditan, 200 mg lasmiditan, and 400 mg lasmiditan. The washout period between each dose should be at least 3 days (72 hours).

Eligible subjects will be admitted to the clinical research unit (CRU) on Day -1 before the planned study drug dosing during each of the dosing periods in both the Qualification Phase and Treatment Phase. After verification of subjects' eligibility, including a urine drug screen at time of CRU admission, blinded study drug will be administered on Day 1 after an overnight fast. Abuse potential will be assessed using Drug Effects VAS Battery. Adverse events (AEs), vital

signs, and electrocardiograms (ECGs) will be monitored, and PK samples will be collected according to the Study Schedule (Section 2 of the protocol).

Follow-up Phase: Subjects will have a follow-up visit approximately 1 week after their last dose of study drug, and will present to the CRU for discharge from the study as deemed appropriate by the investigator. Subjects who discontinued from the study before its completion will be asked to attend an Early Discontinuation visit (according to the Study Schedule [Section 2 of the protocol]) approximately 1 week after the last dose of study drug dosing. Figure 1 illustrates the study design.

Figure 1. Illustration of study design

Screening Phase	Qualification Phase		Treatment Phase					Follow-up Phase
Screening Visit	Period 1	Period 2	Period 1	Period 2	Period 3	Period 4	Period 5	Discharge Visit
								Approx. 1 week
up to 28 days	3 days	3 days	3 days	3 days	3 days	3 days	3 days	after last dose
			Placebo	Las-low	Alprazolam	Las-med	Las-high	
			Las-low	Las-med	Placebo	Las-high	Alprazolam	
			Las-med	Las-high	Las-low	Alprazolam	Placebo	
			Las-high	Alprazolam	Las-med	Placebo	Las-low	
	Alprazolam	Placebo	Alprazolam	Placebo	Las-high	Las-low	Las-med	
	Placebo	Alprazolam	Las-high	Las-med	Alprazolam	Las-low	Placebo	
			Alprazolam	Las-high	Placebo	Las-med	Las-low	
			Placebo	Alprazolam	Las-low	Las-high	Las-med	
			Las-low	Placebo	Las-med	Alprazolam	Las-high	
			Las-med	Las-low	Las-high	Placebo	Alprazolam	

Abbreviations: High = high (400 mg) dose; Las = lasmiditan; Low = low (100 mg) dose; Med = medium (200 mg) dose.

6. TREATMENTS

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

Phase	Study Treatment Name	Treatment order in TFL
Qualification Phase	Placebo	1
	1 mg alprazolam	2
Treatment Phase	Placebo	3
	2 mg alprazolam	4
	100 mg lasmiditan	5
	200 mg lasmiditan	6
	400 mg lasmiditan	7

7. SAMPLE SIZE JUSTIFICATION

The study design and analysis methods are as prescribed in "Assessment of Abuse Potential of Drugs: Guidance for Industry" published by the US Food and Drug Administration (FDA), January 2017 (FDA 2017)[3]. Three different hypothesis tests are of primary interest:

1. Validation test of the sensitivity and integrity of the study: Does the positive control (C) produce mean responses that show greater abuse potential compared to placebo (P)?

$$H1_0: \mu_C - \mu_P \leq \delta_1 \text{ versus } H1_a: \mu_C - \mu_P > \delta_1 \text{ where } \delta_1 > 0$$

2. Does the test drug (T) produce mean responses that show less abuse potential compared to positive control?

$$H2_0: \mu_C - \mu_T \leq \delta_2 \text{ versus } H2_a: \mu_C - \mu_T > \delta_2 \text{ where } \delta_2 \geq 0$$

3. Does the test drug produce mean responses that show similar abuse potential, compared to placebo?

$$H3_0: \mu_T - \mu_P \geq \delta_3 \text{ versus } H3_a: \mu_T - \mu_P < \delta_3 \text{ where } \delta_3 > 0$$

Approximately 60 subjects will be randomly assigned to 1 of 10 treatment sequences, in order to get approximately 50 completers. Subjects who are randomized but who do not complete all 5 periods during the Treatment Phase may be replaced. Replacement subjects will enter the same treatment sequence as the original subject to complete all 5 periods. Treatment sequence assignment will be determined by the repeated Williams square design, as shown in Figure 1.

This will lead to 90% or more power for testing each of the hypotheses of primary interest listed above, with the following assumptions:

- standard deviation of differences of 16 for the Drug Liking VAS (estimate based on within-subject standard deviation estimate of 11.4 from previous studies [Blanchard et al. 2010][4])
- actual mean difference between alprazolam and placebo of 22 or more for the Drug Liking VAS,
- actual mean difference between alprazolam and lasmiditan of 12 or more for the Drug Liking VAS,
- actual mean difference between lasmiditan and placebo of 7 or less for the Drug Liking VAS,
- $\delta_1 = 15$, $\delta_2 = 5$, and $\delta_3 = 14$; and
- one-sided significance level of 0.05.

The margin for comparing alprazolam with placebo (δ_1) is defined as 15 mm, based on the 2017 FDA guidance, stating that there should be a difference of at least 15 points between placebo and positive control response. The margin for comparing alprazolam with lasmiditan (δ_2) is defined as 5 mm, based on the need to show that lasmiditan shows some non-negligible lower abuse potential compared to positive control. The margin for comparing lasmiditan with placebo (δ_3) is defined as 14 mm. Consistent with FDA advice, the margin for comparing lasmiditan with placebo (δ_3) is less than the margin for comparing the positive control (alprazolam) to placebo (δ_1).

8. DEFINITION OF ANALYSIS POPULATIONS

8.1 Populations

The "Safety" population will consist of all subjects who received at least one dose of study drug (lasmiditan, alprazolam, or placebo). This will be the population used for all analyses except the Drug Effects VAS battery analyses and PK/PD analyses.

The "Pharmacodynamic" population will consist of all subjects who received at least one dose of lasmiditan, alprazolam or placebo and have evaluable PD data. This will be evaluated for the Qualification Phase and Treatment Phase separately. 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 time of maximum observed drug concentration (t_{max}).

The "Pharmacokinetic" population will consist of all subjects who received at least one dose of lasmiditan or alprazolam and have evaluable PK data in the Treatment Phase. The PK population is applicable to the Treatment Phase only. Subjects may be excluded from the PK summary statistics and statistical analysis if a subject has an AE of vomiting that occurs at or before 2 times median $t_{max.}$

For the statistical analysis of the Drug Effects VAS Battery in the Treatment Phase, the analysis will be performed only subjects who complete all 5 periods.

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), standard error (SE), first quartile, median, third quartile, 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 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 for the Qualification Phase and Treatment Phase separately using the Safety population. For subjects that don't qualify for the Treatment Phase, the reason for not proceeding to the next phase will be listed. Recreational drug use history will be listed and will include details of the specific substances taken. A summary table and listings of the summary of number of lifetime non-therapeutic experiences with central nervous system (CNS) depressants, number of non-therapeutic experiences with CNS depressants in 12 weeks prior to screening, and lifetime non-therapeutic experiences with other classes of drugs of abuse (with the latter split out by drug class) will be produced.

9.3 Pharmacokinetic Assessment

9.3.1 Pharmacokinetic Analysis

PK assessments and analysis will only be applicable to the Treatment Phase of this study.

PK 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 alprazolam 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 CSR. 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 predose 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 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 predose average concentration for single-dose data from non-endogenous compounds will be set to zero. Otherwise, only quantifiable concentrations will be used to calculate average concentrations.
- Concentrations at a sampling time exceeding the sampling time window specified in the protocol, or ± 10%, will be excluded from the average concentration profiles.
- Concentrations excluded from the mean calculation will be documented in the final study report.
- A concentration average will be plotted for a given sampling time only if 2/3 of the individual data at the time point have quantifiable measurements that are within the sampling time window specified in the protocol or ± 10%. An average concentration estimated with less than 2/3 but more than 3 data points may be displayed on the mean concentration plot if determined to be appropriate and will be documented within the final study report.

Treatment of Outliers during Pharmacokinetic Analysis

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

<u>Data within an Individual Profile</u>

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

- For PK profiles during single dosing of non-endogenous compounds, the concentration in a predose sample is quantifiable.
- For any questionable datum that does not satisfy the above criteria, the profile will be evaluated and results reported with and without the suspected datum.

Data between Individual Profiles

1. If n<6, then the dataset is too small to conduct a reliable range test. Data will be analyzed with and without the atypical value, and both sets of results will be reported.

2. If n≥6, then an objective outlier test will be used to compare the atypical value to other values included in that calculation:

    a. Transform all values in the calculation to the logarithmic domain.

    b. Find the most extreme value from the arithmetic mean of the log transformed values and exclude that value from the dataset.

    c. Calculate the lower and upper bounds of the range defined by the arithmetic mean ±3*SD of the remaining log-transformed values.

    d. If the extreme value is within the range of arithmetic mean ±3*SD, then it is not an outlier and will be retained in the dataset.

    e. If the extreme value is outside the range of arithmetic mean ±3*SD, then it is an outlier and will be excluded from analysis.

If the remaining dataset contains another atypical datum suspected to be an outlier and $n \geq 6$ 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

Plasma concentrations of lasmiditan and alprazolam will be summarized by nominal time point and treatment in a graphical and tabular format.

The primary parameters for analysis will be C_{max} and AUC of lasmiditan and alprazolam. All PK parameters will be listed and summarized by treatment using standard descriptive statistics.

After inspection of the data, additional analyses may be performed to evaluate whether subjective measures, such as VAS and/or AEs, can be correlated with drug levels over time, if warranted.

9.4 Pharmacodynamic Assessment

9.4.1 Pharmacodynamic Analysis

Drug Effects VAS Battery lists a series of Drug Effects VAS measures that evaluate different subjective effects of the abuse potential of the study drug as shown in the table below.

Scale Name	Scale Text	Response Anchors
Drug Liking	At this moment, my liking for this drug is	0: Strong disliking 100: Strong liking
Overall Drug Liking	Overall, my liking for this drug is	
Take Drug Again	I would take this drug again	0: Definitely not 100: Definitely so
Good Effects	I can feel good drug effects	
Bad Effects	I can feel bad drug effects	
Alertness/Drowsiness	I am feeling	0: Very drowsy 100: Very alert
Agitation/Relaxation	My mood is	0: Very relaxed 100: Very agitated
High	I am feeling	0: Not at all high 100: Extremely high
Hallucination	I am experiencing hallucinations	0: Not at all 100: Extremely

The primary objective of the study is to assess the abuse potential of lasmiditan compared to the positive control alprazolam and to placebo using the maximal effect score (E_{max}) of the at-the-moment 100 mm bipolar Drug Liking VAS. The bipolar Drug Liking VAS is consistent with FDA Guidance (January 2017)[3] such that placebo should produce a score between 40 and 60 representing neutral drug-liking (ie, neither like nor dislike); a score of 0 indicates strong disliking, and a score of 100 indicates strong liking.

The remaining questions in the Drug Effects VAS Battery and the Drug Similarity VAS Battery will be assessed as secondary endpoints.

The Drug Similarity VAS Battery is composed of two sets of VAS measures, the baseline set of VAS measures is to determine how familiar the subjects are with various drugs and how similar their most recently received drug is to those. The second set of VAS measures is confined to checking how similar the most recent drug received was to a list of various drugs. The Baseline set of VAS battery questions will be administered in the Qualification Phase and the second set of measures will be administered during the Treatment Phase. In the tables below are the proposed Drug Similarity VAS measures of interest.

Drug Similarity Visual Analog Scale Battery – Baseline	
1	How familiar are you with cocaine (including crack) use? (not applicable)
2	How similar is the drug you most recently received to cocaine (including crack)? (not applicable)
3	How familiar are you with caffeine use? (not applicable)
4	How similar is the drug you most recently received to caffeine? (not applicable)
5	How familiar are you with ecstasy (MDMA) use? (not applicable)
6	How similar is the drug you most recently received to ecstasy (MDMA)? (not applicable)
7	How familiar are you with D-amphetamine or methamphetamine use? (not applicable)
8	How similar is the drug you most recently received to D-amphetamine or methamphetamine? (not applicable)
9	How familiar are you with phencyclidine (PCP) use? (not applicable)
10	How similar is the drug you most recently received to phencyclidine (PCP)? (not applicable)
11	How familiar are you with codeine or morphine use? (not applicable)
12	How similar is the drug you most recently received to codeine or morphine? (not applicable)
13	How familiar are you with herorin use? (not applicable)
14	How similar is the drug you most recently received to herorin? (not applicable)
15	How familiar are you with LDS use? (not applicable)
16	How similar is the drug you most recently received to LDS? (not applicable)
17	How familiar are you with nicotine use? (not applicable)
18	How similar is the drug you most recently received to nicotine? (not applicable)
19	How familiar are you with pseudoephredrine use? (not applicable)
20	How similar is the drug you most recently received to pseudoephredrine? (not applicable)
21	How familiar are you with cannabis use? (not applicable)
22	How similar is the drug you most recently received to cannabis? (not applicable)
23	How familiar are you with benzodiazepine use? (not applicable)
24	How similar is the drug you most recently received to benzodiazepine? (not applicable)
25	How familiar are you with ketamine use? (not applicable)
26	How similar is the drug you most recently received to ketamine? (not applicable)
27	How familiar are you with mushrooms use? (not applicable)
28	How similar is the drug you most recently received to mushrooms? (not applicable)
29	How familiar are you with barbiturates use? (not applicable)
30	How similar is the drug you most recently received to barbiturates? (not applicable)

Drug Similarity Visual Analog Scale Battery	
1	How similar is the drug you most recently received to cocaine (including crack)? (not applicable)
2	How similar is the drug you most recently received to caffeine? (not applicable)
3	How similar is the drug you most recently received to ecstasy (MDMA)? (not applicable)
4	How similar is the drug you most recently received to D-amphetamine or methamphetamine? (not applicable)
5	How similar is the drug you most recently received to phencyclidine (PCP)? (not applicable)
6	How similar is the drug you most recently received to codeine or morphine? (not applicable)
7	How similar is the drug you most recently received to herorin? (not applicable)
8	How similar is the drug you most recently received to LSD? (not applicable)
9	How similar is the drug you most recently received to nicotine? (not applicable)
10	How similar is the drug you most recently received to pseudoephredrine? (not applicable)
11	How similar is the drug you most recently received to cannabis? (not applicable)
12	How similar is the drug you most recently received to benzodiazepine? (not applicable)
13	How similar is the drug you most recently received to ketamine? (not applicable)
14	How similar is the drug you most recently received to mushrooms? (not applicable)
15	How similar is the drug you most recently received to barbiturates? (not applicable)

In the "How similar" questions, a score of 0 indicates definitely not similar, and a score of 100 indicates definitely similar.

In the "How familiar" questions, a score of 0 indicates definitely not familiar to, and a score of 100 indicates definitely familiar.

9.4.2 Pharmacodynamic Statistical Methodology

Descriptive statistics for the Drug Liking VAS will be reported for each treatment and for each paired difference among treatments.

The E_{max} will be derived as the maximum at-the-moment Drug Liking VAS score among all the individual values that are collected at the scheduled assessment timepoints. The time to E_{max} is the corresponding timepoint at which the maximum score occurs. These will be derived for both the Qualification Phase and Treatment Phase separately for each treatment.

A linear mixed-effects model, which includes period, sequence, and treatment as fixed effects, and subject as a random effect will be used to evaluate the hypothesis tests of primary interest at the E_{max} at a significance level of 0.05 (1-sided). The following pairwise comparisons will be made:

- Alprazolam minus placebo, with null hypothesis that the difference is $\leq$ 15 mm;

- Alprazolam minus each dose of lasmiditan, with the null hypothesis that the difference is ≤ 5 mm; and

- each dose of lasmiditan minus placebo, with the null hypothesis that the difference is ≥ 14 mm.

Least square mean estimates and 90% confidence intervals (CI) will be reported for each treatment and for each paired difference among treatments.

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

```
proc mixed data=xxx;
class trtmnt period sequence subject;
model emax = trtmnt period sequence / ddfm=kr alpha=0.1 residual outp=pred;
random subject;
lsmeans trtmnt / pdiff=control alpha=0.1;  /*Produce 90% CI*/
lsmeans trtmnt / pdiff=controll alpha=0.05; /*Test at 0.05 significance 1-sided*/
ods output lsmeans=lsm1;
ods output diffs=diff1;
run;


/* Wilcoxon signed rank test */

proc univariate data=tmax;
    var result;
    ods output Quantiles=quant;
    ods output TestsforLocation=pvalues(where=(test='Signed Rank'));
run;

/* Paired sample t-test */

proc ttest data=all;
    title "Paired sample t-test";
    paired Control * Treatment;
run;
```

In the example SAS code, this is currently presenting a lower-tailed test, however this may need adjusting for some of the comparisons.

The residuals from the mixed-effect model will be investigated for normality using the Q-Q plot. If this normality assumption is not met, paired sample t-test or nonparametric test will be considered based on actual data distributions. For nonparametric analyses, pairwise treatment comparisons will be assessed using the Wilcoxon signed-rank test on the within-subject differences, and median and interquartile range will be reported.

Descriptive statistics for each other element of the Drug Effects VAS Battery, aside from the Drug Liking VAS, and for time to peak effect will be reported for each study phase and treatment. If the normality assumptions of mixed effects model on the residuals are met, a linear mixed-effects model similar to that employed for the E_{max} of Drug Liking VAS will be employed for each other element of the Drug Effects VAS Battery.

Descriptive statistics for each element of the Drug Similarity Visual Analog Scale Battery – Baseline and Drug Similarity Visual Analog Scale Battery will be reported for each study phase and treatment.

The pattern of missing data will be assessed in the population of patients who entered into the treatment phase and took at least 1 dose of study drug in the treatment phase by looking at the trend of dropout rates among the first 4 periods, as well as comparing the dropout rates among the 5 treatments.

A sensitivity analysis will be performed on all patients who entered into the treatment phase and received at least 1 dose of study drug in the treatment phase, regardless of completion of all the 5 periods. The same mixed model and model diagnosis procedure as the primary analysis will be implemented.

9.5 Safety and Tolerability Assessments

9.5.1 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 first dosing of the Qualification Phase. 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 20.0 system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and those considered related to the study drug. Any serious AEs will be tabulated. All AE outputs will be presented by Qualification Phase and Treatment Phase separately. An AE that starts during the Qualification Phase or before the Treatment Phase start will be presented under the Qualification Phase summaries only. In the Treatment Phase outputs, any AEs that are ongoing from the Qualification Phase will be flagged in listings, and excluded from tables.

9.5.2 Concomitant medication

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

9.5.3 Clinical laboratory parameters

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.

9.5.4 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 by study phase. Liver related signs and symptoms data will be summarized by study phase and treatment, and listed, if available.

All hepatic chemistry, hematology, coagulation, and serology data will be summarized by study phase, parameter, and treatment, and listed. Values outside the reference ranges will be flagged on the individual subject data listings.

9.5.5 Vital signs

Vital signs data will be summarized by study phase and treatment together with changes from baseline, where baseline is defined as Day 1 predose for each study phase separately. Figures of mean vital signs and mean changes from baseline profiles by treatment will be presented by study phase and treatment. Furthermore, values for individual subjects will be listed by study phase.

Changes from baseline (predose) will be calculated for vitals signs.

9.5.6 Electrocardiogram (ECG)

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

9.5.7 Columbia-Suicide Severity rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale will be listed for individual subjects.

9.5.8 Other assessments

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

9.5.9 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.

3. [FDA] Food and Drug Administration. Guidance for Industry: Assessment of Abuse Potential of Drugs. January 2017. Available at: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

4. Blanchard RL, Sun H, McCrea JB, Schoedel K, Ngo P, Li X, Panebianco DL, Rosen LB, Sellers E, Murphy MG. A clinical study demonstrates no potential for recreational abuse of telcagepant. *Headache*. 2010;50(Suppl 1):S54

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.”

PPD

Approver: PPD
Approval Date & Time: 07-Sep-2017 16:57:17 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 07-Sep-2017 17:03:39 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 07-Sep-2017 18:39:58 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 11-Sep-2017 12:35:08 GMT
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