H8H-MC-LAHB Protocol

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

NCT03286218

Approval Date: 05-Sep-2017

Protocol H8H-MC-LAHB(c)
A Randomized, Subject- and Investigator-Blind, Placebo- and Active-Controlled Study to Assess the Abuse Potential of Lasmiditan

Confidential Information

Lasmiditan (LY573144)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 24 July 2017
Amendment(a) Electronically Signed and Approved by Lilly: 14 August 2017
Amendment(b) Electronically Signed and Approved by Lilly: 31 August 2017
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 05-Sep-2017 GMT

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Protocol Synopsis

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

Rationale:
Lasmiditan is being developed for the acute treatment of migraine. Because lasmiditan penetrates the central nervous system and adverse events possibly related to abuse have been reported in completed clinical studies, the risk of abuse should be evaluated in accordance with the United States Food and Drug Administration's Guidance for Industry: Assessment of Abuse Potential of Drugs (2017).

Objective(s)/Endpoints:

Objectives	**Endpoints**
Primary To assess the abuse potential of lasmiditan compared to the positive control alprazolam and placebo	The difference in the maximal effect score (E_{max}) during the 24 hours after dosing of the at-the-moment 100-mm bipolar Drug Liking Visual Analog Scale (VAS) scores for: • alprazolam versus placebo • lasmiditan versus alprazolam • lasmiditan versus placebo
Secondary • Further characterize the abuse potential of lasmiditan with additional Drug Effects and Drug Similarity VAS measures • Safety evaluations • Pharmacokinetics of lasmiditan	• Assessing additional Drug Effects and Drug Similarity VAS measures in addition to the time course of the assessments: overall drug liking, take drug again, any effects, good effects, bad effects, alertness/drowsiness, agitation/relaxation, high, hallucination, and similarity. • Treatment-emergent adverse event profiles • Pharmacokinetic parameters: area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max})

Summary of Study Design:

Study H8H-MC-LAHB 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: A screening phase will determine the eligibility of subjects for the study based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG). Subjects who meet the screening criteria will enter the Qualification Phase.

Qualification Phase: This will be a subject- and investigator-blind, placebo-controlled, 2-period crossover study designed to identify subjects who are able to discriminate an alprazolam test dose from placebo. Only subjects who meet alprazolam qualification criteria will be eligible to enter the Treatment Phase.

Treatment Phase: This will be a subject- and investigator-blind, placebo- and active-controlled, 5-period crossover study to evaluate the abuse potential of placebo, alprazolam, and 100-mg, 200-mg, and 400-mg lasmiditan.

Follow-up Phase: Subjects will enter a follow-up phase after their last dose of study drug.

Treatment Arms and Planned Duration for an Individual Subject:
For the 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.

For the Treatment Phase, 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, 100-mg lasmiditan, 200-mg lasmiditan, and 400-mg lasmiditan. The washout period between each dose of at least 3 days (72 hours). A follow-up visit will occur approximately 1 week after the last dose of study drug.

Number of Subjects:
An appropriate number of subjects will be screened to allow for approximately 130 subjects to enter into the Qualification Phase so that approximately 60 subjects are randomized in the Treatment Phase and approximately 50 subjects complete the study. Subjects will be randomly assigned to 1 of 10 treatment sequences, determined by the repeated Williams square design. This will lead to 90% or more power for testing each of the hypotheses of primary interest regarding the Drug Liking Visual Analog Scale (VAS) endpoints.

Statistical Analysis:
Subjects who complete all 5 periods of the Treatment Phase will comprise the completers population; this will be the population used for analyzing the Drug Effects VAS Battery. Descriptive statistics for continuous variables will include mean, standard error, minimum, first quartile, median, third quartile, and maximum. Descriptive statistics for categorical variables include count and percent.

Descriptive statistics for the Drug Liking VAS will be reported for each treatment and for each paired difference among treatments. 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 peak of drug response effects (E_{max}) at a significance level of 0.05 (1-sided).

Descriptive statistics for other measures in the Drug Effects and Drug Similarity VAS Battery, adverse events, safety laboratory parameters, vital signs, Columbia-Suicide Severity Rating Scale (C-SSRS), ECG, and pharmacokinetic parameters will be reported by treatment.

2. Schedule of Activities

2.1. Qualification Phase

Study Schedule Protocol H8H-MC-LAHB: Qualification Phase

Procedure	Screening Phase	Qualification Phase: Periods 1-2				Comment
Study Day	-28 to -2	-1	1	2	D/C or ET	Minimum of 3 days = 72 h washout between doses
Informed Consent	X					
Visits	O	I	I	I	O	I: inpatient; O: outpatient
Medical History	X					
Drug History	X					
Height	X					
Weight	X	X			X	Weight will be collected at screening, Qualification Phase Period 1, and D/C or ET.
ECG	X	X				
Screening Labs	X					
Study Drug Dosing			X			Study drug will be administered on Day 1 after an overnight fast.
AE/Medication Review	X	X	X	X	X	
PE	X	X				Full PE at screening and first CRU admission. Symptom-driven PE at all other time points as deemed necessary by PI.
BP/Pulse	X	X	0, 1, 2, 4, 6	24	X	Single supine BP and pulse rate.
Urine Drug Screen and Alcohol Screen	X	X				Urine Drug and Alcohol screen will be collected at screening and Qualification Phase Period 1 (additional test may be performed at Period 2 if subject discharged between periods).
Pregnancy Test	X	X				Serum test at screening. Serum or urine tests thereafter. Pregnancy test will be collected at screening and Qualification Phase Period 1 (additional test will be performed at Period 2 if subject discharged between periods).
CBC and Chemistry	X	X			X	Performed as a fasting sample on Day -1 of Period 1 only.
VAS training		X				VAS training to occur on Day -1 of each Period
Drug Effects VAS Battery			0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12	24		Overall Drug Liking and Take Drug Again assessed at 12 and 24 hours postdose only.
Drug Similarity VAS Battery				24		Drug Familiarity VAS, a subset of Drug Similarity VAS, will be administered at Day 2 Qualification Phase Period 1 only.
C-SSRS/Self Harm	X	X			X	A self-harm form may be administered at time of C-SSRS. C-SSRS/Self Harm will be administered at screening, Day -1 Qualification Phase of Period 1, and D/C or ET (additional test will be performed at Period 2 if subject was discharged between periods).

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood counts; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D/C = discontinuation; ECG = electrocardiogram; ET = early termination; h = hour; labs = laboratory tests; mins = minutes; PE = physical examination; PI = principle investigator; VAS = visual analogue scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Should be taken in the following order: ECG ± 15 mins, BP/Pulse ± 15 mins, and VAS ± 15 mins at nominal time point.

2.2. Treatment Phase

Study Schedule Protocol H8H-MC-LAHB: Treatment Phase

Procedure	Treatment Phase: Periods 1-5				Follow-up Phase	Comment
Study Day	-1	1	2	D/C or ET	20	Minimum of 3 days = 72 h washout between doses
Visits	I	I	I		O	I: inpatient; O: outpatient; Follow-up = approximately 1 week after last dose of study drug.
Weight	X			X	X	Weight will be collected at Treatment Phase Period 1, D/C or ET, and Follow-up.
ECG	X	0, 2, 4	24	X	X	
Study Drug Dosing		X				Study drug will be administered on Day 1 after an overnight fast.
AE/Medication Review	X	X	X	X	X	
PE	X					Full PE at first CRU admission. Symptom-driven PE at all other time points as deemed necessary by PI.
BP/Pulse	X	0, 1, 2, 4, 6	24	X	X	Single supine BP and pulse rate. Follow same window as PK.
Urine Drug Screen and Alcohol Screen	X				X	Urine Drug and Alcohol screen will be collected at Treatment Phase Period 1 and Follow-up (additional test will be performed at Periods 2-5 if subject discharged between periods).
Pregnancy Test	X				X	Pregnancy test will be collected at Treatment Phase Period 1 only and Follow-up (additional test will be performed at Periods 2-5 if subject discharged between periods).
CBC and Chemistry	X				X	Fasting samples on Days -1 of all periods.
VAS training	X					VAS training to occur on Day -1 of each Period
Drug Effects Battery		0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12	24			Overall Drug Liking and Take Drug Again assessed at 12 and 24 hours postdose only.
Drug Similarity VAS Battery			24			
C-SSRS/ Self-Harm	X			X	X	A self-harm form may be administered at time of C-SSRS. C-SSRS/Self Harm will be administered on Day -1 Treatment Phase Period 1, D/C or ET, and Follow-up (additional test will be performed at Periods 2-5 if subject discharged between periods).
PK		0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24			
Genetic Sample	X					Genetic samples will be collected at the first period of Treatment Phase only.

Abbreviations: AE = adverse event; BP = blood pressure; CBC = complete blood counts; CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D/C = discontinuation; ECG = electrocardiogram; ET = early termination; h = hour; PE = physical examination; PI = principle investigator; PK = pharmacokinetics; VAS = visual analogue scale.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, vital signs, and venipuncture.

[a] Should be taken in the following order: ECG ± 15 mins, BP/Pulse ± 15 mins, PK ± 5 mins, and VAS ± 15 mins at nominal time point.

3. Introduction

3.1. Study Rationale

Lasmiditan is a centrally penetrant, potent, and selective small-molecule 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor agonist. Lasmiditan is being developed by Eli Lilly and Company (Lilly) for the acute treatment of migraine. This molecule has been developed by Lilly as LY573144 and by CoLucid Pharmaceuticals, Inc. (CoLucid) as COL-144.

Because lasmiditan penetrates the central nervous system (CNS) and adverse events (AEs) possibly related to abuse have been reported in completed clinical studies, the risk of abuse will be evaluated in accordance with the United States (US) Food and Drug Administration's (FDA's) Guidance for Industry: Assessment of Abuse Potential of Drugs (FDA 2017).

3.2. Background

Two Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine, using intravenous (IV) and tablet formulations, respectively. One Phase 3 randomized, double-blind, placebo-controlled trial has been completed in the US (COL MIG-301 [SAMURAI]). In the SAMURAI study, both 100- and 200-mg doses of orally administered lasmiditan achieved superior 2-hour pain-free rate and a relief for the most bothersome migraine symptoms compared to baseline.

Five Phase 1 studies of lasmiditan have been completed using IV, sublingual, and oral formulations of lasmiditan in healthy subjects. Single doses of lasmiditan up to 400 mg were tolerated by healthy subjects.

In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1 hour to 2.5 hours after a single oral dose, and the geometric mean terminal half-life was approximately 4 to 6 hours. Lasmiditan exhibited dose-linear pharmacokinetics (PK); low to moderate intersubject variability in exposure was observed across doses (percent coefficient of variation [%CV] up to 61% and 45% for maximum observed drug concentration [C_{max}] and area under the curve [AUC], respectively. Renal clearance of lasmiditan was low, with approximately 2% of the parent dose recovered by 24 hours postdose. Coadministration of lasmiditan with a high fat diet led to a delay in median time to maximum concentration (T_{max}) value by approximately 1 hour and a modest (approximately 20%) increase in C_{max} and AUC values, relative to that under fasted conditions.

Based on the currently available data from in vitro and in vivo studies in humans, lasmiditan appears to be eliminated primarily through both non-cytochrome P450 (CYP) and CYP-mediated metabolism to form metabolites M8 (keto-reduced metabolite), M7 (carbonyl oxidized metabolite), and M18 (keto-reduced, carbonyl oxidized metabolite). All 3 of these major metabolites circulate in humans are not considered to be active, and have been quantitated in pharmacokinetic (PK) studies.

Across the completed Phase 1, 2, and 3 clinical studies, doses of 0.1 to 400 mg of lasmiditan were evaluated in healthy subjects or patients with migraine; methods of administration included

IV, oral, and sublingual. Compared with placebo, the most frequently reported treatment-emergent adverse events (TEAEs) that could possibly indicate abuse potential after receiving lasmiditan included somnolence, fatigue, dizziness, and hot flash. Less frequently reported TEAEs possibly related to abuse after receiving lasmiditan included euphoric mood, hallucination, and feeling abnormal. A majority of these TEAEs were mild or moderate in severity and none led to subjects' withdrawal. One subject experienced a serious adverse event (SAE) of dizziness that was moderate in severity (lasmiditan 200 mg; COL-MIG 202).

Nonclinical receptor-binding results indicated that with the exception of the 5-HT_{1F} receptor subtype, lasmiditan and its major metabolites (M7, M8, and M18) do not demonstrate affinity for 5-HT_1 serotonin receptor subtypes. Lasmiditan also had poor affinity for the benzodiazepine binding site on the gamma-aminobutyric acid $(GABA)_A$ ionophore. Additionally, in a rat drug discrimination study, in which lorazepam served as a positive control, none of the lasmiditan doses tested (10, 30, and 100 mg/kg) produced a discriminative stimulus similar to lorazepam.

3.3. Benefit–Risk Assessment

This study compares the abuse potential for lasmiditan versus placebo, and versus alprazolam in experienced recreational polydrug users. Thus, there is no anticipated therapeutic benefit for the subjects in this study.

To date, lasmiditan has been tolerated by healthy subjects after single dose oral administration up to 400 mg. The most frequently reported AEs in clinical studies include somnolence, dizziness, fatigue, and hot flash. More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of lasmiditan are to be found in the Investigator's Brochure (IB).

Alprazolam, a short-acting benzodiazepine, has been chosen as a positive control. Potential risks from alprazolam include sedation and somnolence. Administration of lasmiditan and alprazolam will be conducted in inpatient setting, with monitoring of adverse reactions, vital signs, and electrocardiograms (ECGs). Adverse events will be managed with supportive care.

Only subjects with a prior history of recreational drug use will be enrolled in this study and a maximum of 2 doses within the therapeutic dose range of alprazolam will be administered to minimize potential risks, including the risk for dependence. Subjects at risk of adverse reaction from alprazolam, including subjects with a prior history of benzodiazepine dependence, seizures, or depression and concomitant use of CYP3A inhibitors will be excluded from the study. Information about known risks for alprazolam can be found in the package insert for alprazolam.

4. Objectives and Endpoints

Table LAHB.1 shows the objectives and endpoints of the study.

Table LAHB.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the abuse potential of lasmiditan compared to the positive control alprazolam and placebo	The difference in the maximal effect score (E_{max}) during the 24 hours after dosing of the at-the-moment 100-mm bipolar Drug Liking Visual Analog Scale (VAS) scores for: • alprazolam versus placebo • lasmiditan versus alprazolam • lasmiditan versus placebo
Secondary • Further characterize the abuse potential of lasmiditan with additional Drug Effects and Drug Similarity VAS measures • Safety evaluations • Pharmacokinetics of lasmiditan	• Assessing additional drug effects and drug similarity VAS measures in addition to the time course of the assessments: overall drug liking, take drug again, any effects, good effects, bad effects, alertness/drowsiness, agitation/relaxation, high, hallucination, and similarity. • Treatment-emergent adverse event profiles • Pharmacokinetic parameters: area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max})
Tertiary/Exploratory Pharmacokinetics of alprazolam	• Pharmacokinetic parameters: AUC and C_{max}

5. Study Design

5.1. Overall 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 Visual Analog Scale (VAS). Only subjects who meet alprazolam qualification criteria (see Section 6.1.1) will be eligible to enter the Treatment Phase.

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

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]) approximately 1 week after the last dose of study drug dosing.

Study governance considerations are described in detail in Appendix 3.

Figure LAHB.1 illustrates the 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.

Figure LAHB.1. Illustration of study design for Protocol H8H-MC-LAHB.

5.2. Number of Participants

An appropriate number of subjects will be screened to allow for approximately 130 subjects to enter into the Qualification Phase so that approximately 60 subjects are randomized in the Treatment Phase and approximately 50 subjects complete the study. For the purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been finished.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

This study is designed based on the FDA's Guidance for Industry: Assessment of Abuse Potential of Drugs (FDA 2017[WWW]).

5.4.1. Study Population

The population for this study is recreational poly-drug users who are able to discriminate between alprazolam and placebo. The selection of this population ensures that the subjects are familiar with the psychoactive effects of the positive control to improve the sensitivity for detecting any abuse potential for lasmiditan. In addition, subjects with prior experience of recreational use of sedative medications are more likely to tolerate alprazolam. Lilly or its designee will attempt to enroll a comparable number of men and women, where possible.

5.4.2. Selection of Positive Control

The AE data suggested that the predominant AEs for lasmiditan were sedative effects, including somnolence, with occasional subjects/patients also reporting euphoric-related terms, including euphoric mood and hallucination. Alprazolam has been shown to be able to produce both sedative and euphoric type of symptoms (Zawertailo et al. 1995).

Furthermore, lasmiditan and alprazolam have similar PK profiles. Following oral administration, alprazolam is readily absorbed. Peak concentrations in the plasma occur in 1 to 2 hours following administration. Plasma levels are proportionate to the dose given; over the dose range of 0.5 to 3.0 mg, peak levels of 8.0 to 37 ng/mL were observed. The mean plasma elimination half-life of alprazolam is about 11.2 hours (range: 6.3 to 26.9 hours) in healthy adults. The median T_{max} value of lasmiditan was approximately 1 hour to 2.5 hours, and mean terminal half-life was approximately 4 to 6 hours after oral dosing.

The similarity of both PK and AE profiles of alprazolam and lasmiditan makes alprazolam an appropriate positive control for this study.

Alprazolam has demonstrated abuse potential consistent with other drugs in the benzodiazepine class of compounds and is scheduled under the Controlled Substance Act as a C-IV.

5.4.3. Overall Study Design

The abuse potential will be assessed using a Drug Effects VAS Battery (Section 9.6.1). Due to the subjective nature of these endpoints, the design is subject- and investigator-blind. Subjects and the investigator will be informed of the treatments to be tested in the study; they will be blind to the treatment assignment at each period, which reduces the expectation bias. The crossover design minimizes the inter-individual variability and improves the sensitivity for detecting any differences between treatments. Previous studies on alprazolam suggest that the drug-liking effects reduced to neutral about 24 hours after a 1-mg to 3-mg dose, indicating that a 3-day washout period for the Qualification Phase will be adequate (Levy-Cooperman et al. 2016). Based on the PK properties of lasmiditan, a washout period of at least 3 days is deemed adequate for the Treatment Phase; major metabolites are not considered active.

5.5. Justification for Dose

5.5.1. Lasmiditan

Three single doses of 100, 200, and 400 mg lasmiditan have been selected for this protocol.

Lasmiditan is being evaluated in patients with migraine at 50, 100, and 200 mg in the Phase 3 program. The likely commercial dose levels are 100 and 200 mg based on data from the Phase 2 study (COL MIG-202) and the concluded Phase 3 study (SAMURAI). The 400-mg dose level is the highest oral dose tested in the lasmiditan clinical program to date. This dose has been tolerated by both healthy subjects and patients with acute migraine attacks. It represents 2 times the highest proposed commercial dose of 200 mg, which is consistent with the recent FDA guidance for identifying a supratherapeutic dose for evaluation in a human abuse potential study.

At a 400-mg dose, CNS AEs that may suggest abuse potential, including somnolence, dizziness, euphoria, and hallucination, have been reported in healthy subjects (thorough QT [TQT] Study COL MIG-105) and migraine patients.

5.5.2. Alprazolam

In this single-dose study, a 1-mg dose of alprazolam will be tested in the Qualification Phase and 2-mg doses of alprazolam will be tested in the Treatment Phase.

Clinical studies demonstrated the abuse potential of a single dose of immediate-release alprazolam between the dose range of 1 to 4 mg (Mumford et al. 1995). Drug-liking effects of alprazolam were numerically higher with a higher dose within the 1- to 4-mg dose range using the categorical scale (Evans et al. 1994; Mumford et al. 1995).

The use of different dose levels between the Qualification Phase and Treatment Phase is consistent with precedent (Blanchard et al. 2010) and ensures that the subjects enrolled into the Treatment Phase can safely tolerate and are sensitive to the effects of the positive control. This will help to ensure that subjects can perform the tests and that significant liking is detectable in this study. Using bipolar Drug Liking VAS, the drug-liking effects between 1- and 3-mg alprazolam was modest (2 to 4 mm) (Blanchard et al. 2010; ClinicalTrials.gov [WWW]). Therefore, only 1 dose of 2-mg alprazolam will be evaluated in the Treatment Phase as positive control.

The 1- and 2-mg doses are within the therapeutic dose range of alprazolam (Xanax® US package insert, 2011). Risk and severity of dependence appear greater in patients treated with alprazolam doses >4 mg/day and for periods of >12 weeks (Xanax US package insert, 2011). Higher doses of alprazolam are also associated with other adverse effects, such as more severe sedation and somnolence. Thus, higher doses beyond 2 mg are not proposed for this study.

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and ECG.

Abnormal screening tests (including, but not limited to physical examination, screening laboratory tests, vital signs, and ECG) may be repeated based on the investigator's judgment.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur up to 28 days prior to the Qualification Phase. Subjects who do not enter the Qualification Phase within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening:

[1] are overtly healthy males or females, as determined by medical history and physical examination

[1a] female subjects:

- Women not of childbearing potential may participate and include those who are:
    A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Müllerian agenesis; or
    B. postmenopausal – defined as either
        i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either: a) cessation of menses for at least 1 year, or b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
        ii. A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
        iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

- Women of childbearing potential who are abstinent (if this is complete abstinence as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males.

- Otherwise, women of childbearing potential (WOCBP) participating must agree to use 2 forms of effective contraception, where at least 1 form is highly effective (less than 1% failure rate), for the entirety of the study. Contraception must continue for 1 month following completion of study drug administration.
    a. WOCBP must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative pregnancy test (serum or urine tests) within 24 hours prior to exposure. Subsequent pregnancy testing (urine or serum tests) should be completed monthly.
    b. Two forms of effective contraception, where at least one form is highly effective (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) will be used. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

[2] are 18 to 55 years of age inclusive at time of consent

[3] have a body mass index of 18 to 32 kg/m^2, inclusive

[4] have clinical laboratory test results within normal reference range, or results with acceptable deviations that are judged to be not clinically significant by the investigator

[5] have venous access sufficient to allow for blood sampling as per the protocol

[6] are able and willing to give signed informed consent, are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures

[7] Subjects must be recreational drug users defined as follows:

- ≥10 lifetime non-therapeutic experiences (ie, for psychoactive effects) with central nervous system (CNS) depressants (eg., benzodiazepines, barbiturates, zolpidem, eszopiclone, propofol/fospropofol, gamma-hydroxy-butyrate)
- ≥1 non-therapeutic use of a CNS depressant/sedative drug within the 12 weeks prior to Screening.
- ≥1 lifetime non-therapeutic use of another drug class of abuse (eg, opioids, stimulants, dissociatives, or hallucinogens).

[8] agree not to consume any recreational drugs during the study.

6.1.1. Qualification Criteria

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".
- ≥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 pharmacodynamic assessments within 4 hours post-dose.
- 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.

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

[9] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

[10] are Lilly or Covance employees

[11] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[12] have been dosed with an investigational drug within the 30 days prior to admission during the Qualification Phase.

[13] have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received the investigational product.

[14] have known allergies to lasmiditan, alprazolam, related compounds, or any components of the formulation, or a history of significant atopy.

[15] has evidence of drug or alcohol dependence (excluding nicotine and/or caffeine) within the past 1 year as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision (DSM-IV-TR), or has a lifetime history of participation in a drug rehabilitation program, excluding past participation in tobacco smoking cessation programs or previous court mandated treatment.

[16] are currently seeking or participating in treatment for addiction or substance-related disorders, or have recovered from substance abuse disorder.

[17] have a significant history of or current cardiovascular (including arrhythmia, bradycardia, heart block), respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data.

[18] have a history of significant psychological illness, including any affective disorders within the past year, or are currently taking medications for psychological illness, including selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or tricyclic antidepressants.

[19] are currently taking prescription or over-the-counter (OTC) medications other than those that are permitted (as outlined in Section 7.7).

[20] Positive test results for human immunodeficiency virus- (HIV-) 1/HIV-2 antibodies, Hepatitis B surface antigen (HBsAg) or Hepatitis C virus antibody (HCVAb).

[21] are women who are lactating.

[22] have a history of significant sleep disorder, including sleep apnea or narcolepsy.

[23] have donated blood of more than 500 mL within the previous 4 weeks of study screening.

[24] have an average weekly alcohol intake that exceeds 21 units per week for males, and 14 units per week for females, or are unwilling to follow study alcohol restrictions (refer to Section 6.3.2).

[25] have a history of orthostatic hypotension, vertigo, syncopy, or presyncopy

[26] have a history of brain injury, including a history of concussions.

[27] take medications or other substances that affect CYP3A activity within 14 days of screening.

[28] in the opinion of the investigator are considered to be a danger to themselves, or who have answered "yes" to either Question 4 or Question 5 on the Suicidal Ideation portion of the C-SSRS; or answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of C-SSRS, and the ideation and behavior occurred within the past 6 months.

[29] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, subjects may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Subjects are prohibited from consumption of grapefruit, grapefruit juice, and Seville (blood) oranges and their juice during the entire duration of the study. Subjects should only consume meals/snacks provided by the CRU during inpatient stays. Subjects should fast from midnight on Day -1 up to the time of dosing.

6.3.2. Caffeine, Alcohol, and Tobacco

6.3.2.1. Caffeine and Alcohol

Subjects may be allowed 2 servings of a caffeinated beverage during inpatient days.

The use of alcohol is not allowed from 24 hours before all study visits and during the inpatient clinic stays. At all other times, alcohol consumption is limited to no more than 2 alcoholic beverages or the equivalent per day. Breath alcohol tests or the equivalent will be performed as shown in the Schedule of Activities (Section 2).

6.3.2.2. Tobacco

Subjects must adhere to smoking restrictive rules of CRU during the inpatient stays and at outpatient visits.

6.3.3. Activity

Subjects must refrain from strenuous exercise throughout the study. Subjects should not be allowed to drive or operate machinery, unless deemed appropriate by the investigator.

6.3.4. Contraception Requirement

See Inclusion Criteria [1] (Section 6.1) for details on the use of contraception during the study.

6.3.5. Use of Drugs of Abuse

Subjects will be instructed to refrain from recreational drug use for the duration of the study (from screening through the last treatment period), including cannabinoid use. While a positive cannabinoid test may not exclude the subject from further participation, the subject will be informed that there is a safety risk of using recreational drugs during the study and that an

adverse interaction with a recreational drug is possible. If a subject reports to the clinical research facility and has a positive cannabinoid test, the subject will be required to pass a Cannabis Intoxication Evaluation to confirm that he/she is not cognitively impaired or intoxicated. Following this evaluation, continued eligibility will be at the discretion of the Investigator.

A subject with a positive result on the screen for substances of abuse, other than cannabinoids, may be rescheduled and retested up to 3 times at the discretion of the Investigator. If the subject continues to have positive results, he/she will be discontinued from the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

7. Treatment

7.1. Treatment Administered

This study compares single doses of orally administered lasmiditan at 100, 200, and 400 mg with placebo and alprazolam.

Table LAHB.2 shows the treatment regimens.

Qualification Phase: 1 tablet of alprazolam or placebo will be administered orally with approximately 240 mL of room temperature water in the morning, in a sitting position, after an overnight fast.

Treatment Phase: An appropriate number of lasmiditan, alprazolam, and/or placebo tablets will be administered orally with approximately 240 mL of room temperature water, in the morning of each dosing day, in a sitting position, after an overnight fast. The total number of tablets administered in each of the 5 dosing periods will be the same.

Study drugs (alprazolam, lasmiditan, and/or placebo) will be prepared into individual dispensing cups by an unblinded pharmacist and administered by an unblinded staff member who will not be involved in any study assessment procedures. Subjects will be blindfolded prior to each dosing session for each period during the Qualification and Treatment Phases. The unblinded staff member will hand the dispensing cup to each subject, who will then self-administer all tablets in the dispensing cup without touching any of the tablets by hand. Neither the Investigator nor any nursing staff involved in the subject assessment will be allowed to witness the study drug administration.

For both phases, water will be allowed 1 hour after study drug dosing, and meals will be allowed approximately 2 hours after study drug dosing. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table LAHB.2. Treatments Administered

Treatment Name	Lasmiditan	Placebo	Alprazolam
Dosage Formulation	Tablet	Tablet	Tablet
Unit dose Strength(s)/Dosage Level(s)	100-mg, 200-mg tablets	Placebo to match lasmiditan	1-mg or 2-mg tablet
Route of Administration	Oral	Oral	Oral

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly

- maintaining accurate records of investigational product dispensing and collection
- returning all unused medications to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

Each lasmiditan tablet contains 100 or 200 mg of active ingredient and is provided as bulk supply in bottles. Placebo tablets look identical to 100- or 200-mg lasmiditan, but contain no active ingredient, and will be provided in similar bulk bottles.

Alprazolam will be obtained from commercial source. The details and presentation of alprazolam will be provided prior to document finalization.

The investigational product will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Treatment sequences will be determined using a repeated 5×5 Williams square design (Figure LAHB.1). The study will be conducted at a single study center, so the respective randomization schedule can be securely maintained by the study center pharmacist who is responsible for dispensing the blinded study medication in accordance with the schedule. The sponsor (or designee) will be responsible for generating each of the randomization schedules and distributing them directly to the study center pharmacist.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

7.3. Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

Emergency codes will be available to the investigator. A code, which reveals the treatment assignment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from further drug administration, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study subject's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The

subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

Not applicable.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm that appropriate temperature conditions have been maintained, as communicated by the sponsor, during transit for all investigational products received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational products or study materials, and only authorized site staff may supply or administer investigational product. All investigational products should be stored in an environmentally controlled and monitored (manual or automated) area, in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Subjects on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Any concomitant medication must be documented in the CRF.

Drugs, or supplements that are known inducers, or inhibitors of CYP3A are specifically excluded. Additional drugs are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

At least 14 days prior to the Qualification Phase and during the course of the entire study, subjects should not take any new prescribed medications. Over the counter (OTC) medications, vitamins, or herbal supplements other than those permitted at the time of screening will not be permitted for 7 days prior to the Qualification Phase and during the course of the entire study. Medications with psychoactive properties include, but are not limited to, anxiolytics, antidepressants, anticonvulsants, antipsychotics, medical cannabis, OTC diet or sleep aids, histamine antagonists, cough/cold/sinus preparations, steroids, narcotic analgesics, and

phosphodiesterase 5 inhibitors. Medications for weight loss or smoking cessation are specifically excluded.

In general, concomitant medication should be avoided; however, acetaminophen (maximum 2 g/24 hours) may be administered at the discretion of the investigator for treatment of headaches, or minor pain or fever, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP or designee. Any medication used during the course of the study must be documented in the CRF.

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing from the treatment prematurely for any reason should complete AE and other follow-up procedures per Section 2 of this protocol.

Subjects discontinuing from the study prematurely for any reason must complete AE and follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Subjects will be discontinued from the investigational product under the following circumstances:

- Subjects who experience an SAE, regardless of causality
- Subjects who experience a sustained moderate or severe AEs that require medical intervention

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist or CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist or CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator or designee decision
    - the investigator decides that the subject should be discontinued from the study
    - if the subject, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
    - Physician decision
    - Protocol violation
    - AE

  - Death
  - Study terminated by Sponsor
  - Met protocol defined discontinuation criteria
  - Other
- Subject Decision
  - the subject requests to be withdrawn from the study

If a subject withdraws from the study, the investigator or designee will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the investigator or designee will follow the subject until the AE has resolved or stabilized. All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study.

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject.

The investigator is responsible for the appropriate medical care of subjects during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the subject to discontinue the investigational product before completing the study. The subject should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the informed consent form (ICF) is signed, study site personnel will record, via electronic data entry, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a potential cause-and-effect relationship between the AE and the investigational product, study device, and/or study procedure.

Planned surgeries should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a subject's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry.

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in one of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly CRP/clinical pharmacologist, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued from and/or completed the study (the subject summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to the investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB, and that the investigator reports as related to the investigational product or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product (or drug delivery system) so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of lasmiditan or alprazolam is considered any dose higher than the dose assigned through randomization.

Refer to the lasmiditan IB for information on the clinical consequences of an overdose. Refer to the alprazolam US Package Insert for information on overdose.

9.4. Safety

9.4.1. Laboratory Tests

For each subject, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the study.

9.4.2. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.3. Vital Signs

For each subject, vital sign measurements should be conducted according to the Schedule of Activities (Section 2).

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 2 minutes. If the subject feels unable to stand, supine vital signs only will be recorded.

Additional vital signs may be measured during each study period, if warranted.

9.4.4. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities (Section 2).

Any clinically significant findings from ECGs that result in a diagnosis, and that occur after the subject receives the first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via electronic data entry.

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for at least 5 minutes before ECG collection and remain supine, but awake, during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms will be interpreted by the investigator, or qualified designee, at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT [QTc] interval from baseline) after enrollment, the investigator will determine if the subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.5. Columbia Suicide Severity Rating Scale and Self-Harm Form

The Columbia Suicide Severity Rating Scale (C-SSRS) (Posner 2007; Posner et al. 2007a, Posner et al. 2007b) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS and a corresponding Self-Harm Supplement Form will be administered at the times specified in the Schedule of Activities (Section 2). If a self-harm event is reported, investigators will also complete the Self-Harm Follow-Up Form. If the subject does not attend the discontinuation visit, the C-SSRS and Self-Harm Supplement Form should still be completed if the site has become aware of a suicide-related thought or behavior by other communications. If a self-harm or suicidal-related event is considered serious by the investigator, it must be reported as an SAE via the procedures indicated in Section 9.2. The C-SSRS, Self-Harm Supplement Form, and Self-Harm Follow-Up Form must be administered by appropriately trained site personnel. Any significant change would necessitate a referral to a psychiatrist.

9.4.6. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study. Lilly will review SAEs within the time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes

- adverse events

When appropriate, the Lilly clinical pharmacologist or CRP will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, additional analyses of the safety data will be conducted by the personnel included in the Blinding Plan.

9.4.6.1. Hepatic Safety

If a study subject experiences elevated alanine aminotransferase (ALT) ≥3X upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2X ULN, or elevated total bilirubin level (TBL) ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase (AST), ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly clinical pharmacologist or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine the plasma concentrations of lasmiditan and alprazolam. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor, and stored at a facility designated by the sponsor.

Concentrations of lasmiditan and alprazolam will be assayed using validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) methods. Samples will only be analyzed for the drug administered. Samples collected to maintain the blinding will not be analyzed.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following the last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein binding work.

9.6. Pharmacodynamics – Abuse Potential Assessments

9.6.1. Drug Effects and Drug Similarity Visual Analog Scale Battery

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.

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) 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.

Subjects must draw a point on a 100-mm horizontal line that best represents their response to the given question. The endpoints of each electronic scale are marked with descriptive anchors on a scale from 0 to 100 (Fraser et al. 1961; Bond and Lader 1974; Bigelow 1991; Shram et al. 2010).

The VAS measurements should be conducted according to the Schedule of Activities (Section 2).

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research, either now or in the future. Samples will be used to investigate variable exposure or response to lasmiditan and to investigate genetic variants thought to play a role in migraine or substance abuse. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the subject number. These samples and any data generated can be linked back to the subject only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or institutional review boards impose shorter time limits, for the

study at a facility selected by Lilly. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of lasmiditan or after lasmiditan is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of the technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The study design and analysis methods are as prescribed in "Assessment of Abuse Potential of Drugs: Guidance for Industry" published by the US FDA, January 2017 (FDA 2017). 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)?

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

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

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

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

   $H3_0$: $\mu_T - \mu_P \geq \delta_3$ versus $H3_a$: $\mu_T - \mu_P < \delta_3$ 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 subjects to complete all 5 periods. Treatment sequence assignment will be determined by the repeated Williams square design, as shown in Figure LAHB.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])
- 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).

10.2. Populations for Analyses

Subjects who complete all 5 periods of the Treatment Phase will comprise the Completers population; this will be the population used for analyzing the Drug Effects VAS Battery. Pharmacokinetic/Pharmacodynamic (PK/PD) analyses will be conducted on data from all subjects who receive at least 1 dose of lasmiditan or alprazolam and have evaluable PK. All subjects who take at least 1 dose of the investigational product will comprise the safety population; this will be the population used for all analyses except the Drug Effects VAS Battery analyses and PK/PD analyses.

10.2.1. Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The subject's year of birth, sex, weight, height, and other demographic characteristics will be recorded. Age and body mass index will be calculated. Demographic and baseline characteristics will be summarized.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee. A complete list of planned tables, figures, and listings will be included in a separate Statistical Analysis Plan.

Descriptive statistics for continuous variables will include mean, standard error, minimum, first quartile, median, third quartile, and maximum. Descriptive statistics for categorical variables include count and percent. Additional exploratory analyses of the data will be conducted, as deemed appropriate.

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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed by treatment, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment period will be presented by severity and by association with the investigational product as perceived by the investigator. Symptoms reported to occur prior to study entry will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities (MedDRA).

The number of investigational product-related SAEs will be reported by treatment.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, C-SSRS, and ECG parameters. The parameters will be listed and summarized by treatment, using standard descriptive statistics. Additional analyses will be performed, if warranted, upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

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

Pharmacokinetic parameter estimates for lasmiditan and alprazolam will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and AUC of lasmiditan and alprazolam. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported. The parameters will be listed and summarized by treatment using standard descriptive statistics.

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.

10.3.3. Abuse Potential Analyses

Descriptive statistics for the Drug Liking VAS will be reported for each treatment and for each paired difference among treatments. 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 peak of drug response effects (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 ≤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 will be reported for each treatment and for each paired difference among treatments.

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 intraquartile range will be reported.

Descriptive statistics for each other element of the Drug Effects VAS Battery, aside from Drug Liking VAS, and for time to peak effect will be reported for each treatment. If the normality assumptions of mixed-effects model on the residuals are met, a linear mixed-effects model, which includes period, sequence, and treatment as fixed effects, and subject as a random effect will be used to provide least square mean estimates and 90% confidence intervals for each treatment. The residuals from the mixed-effect model will be investigated for normality using the Q-Q plot. If the normality assumptions of mixed-effects model are not met, alternative approaches such as paired t-test or non-parametric test may be considered based on the actual data distributions. For non-parametric analyses, the median and intra-quartile range will be reported for each treatment.

10.3.4. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP/investigator, or designee will consult with the appropriate medical director, or designee, to determine if it is necessary to amend the protocol.

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Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the drug plasma concentration versus time curve
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his/her staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/or his/her staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BUN	blood urea nitrogen
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum concentration
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety, effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to verify that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
C_{max}	maximum observed drug concentration
COL-144	lasmiditan (also LY573144)

Term	Definition
CPK	creatine phosphokinase
CRF	case report form
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	coefficient of variation
CYP	cytochrome P450
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision
ECG	electrocardiogram
E_{max}	maximal effect score
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GABA	gamma aminobutyric acid
GCP	good clinical practice
GGT	gamma glutamyl transferase
HBsAG	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation

Term	Definition
Ig	immunoglobulin
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
INR	international normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board (also ethical review board)
IV	intravenous
LC/MS/MS	liquid chromatography-tandem mass spectrometry
legal representative	An individual or a judicial or other body authorized, under applicable law, to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
Lilly	Eli Lilly and Company
LY573144	lasmiditan (also COL-144)
MedDRA	Medical Dictionary for Regulatory Activities
OTC	over-the-counter
QTc	corrected QT interval
randomization	The process of assigning subjects/patients to an experimental group on a random basis.
RBC	red blood cell
PK	pharmacokinetic
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin level

Term	Definition
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
T_{max}	time after administration of drug when maximum plasma concentration is reached; rate of absorption equals the rate of elimination
TQT	thorough QT study
ULN	upper limit of normal
VAS	Visual Analog Scale
WBC	white blood cell
WOCBP	woman/women of childbearing potential

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Glucose [random and fasting]
Mean cell hemoglobin concentration	
Leukocytes (WBC)	
Platelets	
Differential WBC [absolute counts and %] of:	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	Total protein
Monocytes	Albumin
Eosinophils	Total bilirubin
Basophils	Alkaline phosphatase (ALP)
	Aspartate aminotransferase (AST)
Urinalysis[a]	Alanine aminotransferase (ALT)
Specific gravity	Creatinine
pH	
Protein	
Glucose	
Ketones	Ethanol testing[a,b]
Bilirubin	Urine drug screen[a,b]
Urobilinogen	Hepatitis B surface antigen[a]
Blood	Hepatitis C antibody[a]
Nitrite	HIV
	Pregnancy test [if applicable]
	FSH [if applicable][a]
	Thyroid-stimulating hormone[a]

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cell; WBC = white blood cell.

[a] Performed at screening only.

[b] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities (Section 2); urine drug screen is not conducted at the clinical research unit in Singapore.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Lilly or its designee will attempt to enroll a comparable number of men and women where possible. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly, or its representatives, must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with the protocol and with:

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third-party organization.

Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, the principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator, or designee, will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly, or its representatives, will periodically check a sample of the subject data recorded against source documents at the study site. The study may be audited by Lilly and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of subject personal information collected will be provided in a written document to the subject by the Sponsor.

Study and Site Closure

Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Discontinuation of the Study

The study will be discontinued if Lilly, or its designee, judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly or its designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear Antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth Muscle Antibody (or Anti-actin**
CPK	**Antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol H8H-MC-LAHB Sampling Summary (5 Periods)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	17.5	1	17.5
Clinical laboratory tests[a]	9	8	72
Pharmacokinetics for lasmiditan	2	60 (+3)	120 (6)
Pharmacokinetics for alprazolam	2	60 (+3)	120 (6)
Blood discard for cannula patency	1	60	60
Pharmacogenetics	10	1	10
Total			411.5
Total for clinical purposes [rounded up to nearest 10 mL]			420

[a] Additional samples may be drawn, if needed, for safety purposes.

Appendix 6. Protocol Amendment H8H-MC-LAHB(c) Summary: A Randomized, Subject- and Investigator-Blind, Placebo- and Active-Controlled Study to Assess the Abuse Potential of Lasmiditan

Overview

Protocol H8H-MC-LAHB - A Randomized, Subject- and Investigator-Blind, Placebo- and Active-Controlled Study to Assess the Abuse Potential of Lasmiditan - has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

The following change was made to this protocol and rationale is as follows:

- Appendix 5 Blood Sampling Summary updated to include blood volumes for items previously listed as to be determined to ensure consistency with CRU procedure and alignment with the informed consent form.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol H8H-MC-LAHB Sampling Summary (5 Periods)

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	~~TBD~~17.5	~~TBD~~ 1	~~TBD~~ 17.5
Clinical laboratory tests[a]	~~TBD~~ 9	~~TBD~~ 8	~~TBD~~ 72
Pharmacokinetics for lasmiditan	2	60 (+3)	120 (6)
Pharmacokinetics for alprazolam	2	60 (+3)	120 (6)
Blood discard for cannula patency	1	60	60
Pharmacogenetics	10	1	10
Total			~~TBD~~ 411.5
Total for clinical purposes [rounded up to nearest 10 mL]			~~TBD~~ 420

~~Abbreviations: TBD = to be determined~~

[a] Additional samples may be drawn, if needed, for safety purposes.

PPD

Approver: PPD
Approval Date & Time: 05-Sep-2017 19:17:02 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 05-Sep-2017 20:05:29 GMT
Signature meaning: Approved