Protocol Protocol H8H-MC-LAHE(b)
Multiple-Ascending Dose, Safety, Tolerability, Pharmacokinetic, and Drug-Drug Interaction Study of Lasmiditan

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Confidential Information

Lasmiditan (LY573144)

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1. Protocol Synopsis

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

Objective(s)/Endpoints:

Objectives	Endpoints
Primary The primary objective of this study is to explore the safety and tolerability of multiple doses of 200 mg and 400 mg lasmiditan in healthy subjects.	Incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).
Secondary • To evaluate the plasma pharmacokinetics (PK) of multiple doses of lasmiditan and its major metabolites.	Maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), area under the concentration versus time curve (AUC) over one dosing interval (AUC_τ).
• To evaluate the effect of multiple doses of lasmiditan on CYP1A2, CYP2C9, and CYP3A activity.	C_{max}, T_{max}, AUC from time zero to infinity (0-∞), and AUC from time zero to last observable concentration AUC(0-t_{last}) of probe drugs.
• To evaluate any potential withdrawal symptoms following once-daily dosing of lasmiditan.	Responses to the benzodiazepine withdrawal symptom questionnaire and physician withdrawal checklist.

Summary of Study Design:

This is a Phase 1, randomized, subject and investigator-blinded, placebo-controlled, multiple-ascending dose study, conducted in 2 cohorts of healthy subjects. The study will evaluate the safety, tolerability and PK of lasmiditan following once-daily dosing of 200 and 400 mg. The potential effects of lasmiditan upon cytochrome P450 (CYP) induction will be evaluated through the PK of components of a coadministered cocktail of CYP substrate drugs (Cohort 1) and measurement of CYP3A-mediated cortisol metabolism (Cohorts 1 and 2).

Treatment Arms and Planned Duration for an Individual Subject:

All subjects will participate in a screening visit up to 28 days prior to study drug dosing.

Subjects will participate in 1 dosing period. Subjects in Cohort 1 will be admitted to the clinical research unit (CRU) on Day -4. Each subject will receive a single dose of probe drug cocktail on Day -3 and Day 7 relative to the first dose of lasmiditan. Subjects will receive a once-daily dose of 200 mg lasmiditan or placebo on Days 1 to 7 of the study. Subjects will be discharged from the CRU on Day 9 of the dosing period, based on investigator discretion.

Subjects in Cohort 2 will be admitted to the CRU on Day -1. Subjects will receive a once-daily dose of 400 mg lasmiditan or placebo on Days 1 to 7 of the study. Subjects will be discharged from the CRU on Day 9 of the dosing period, based on investigator discretion.

All subjects will attend a follow-up visit and be discharged from the study approximately 14 days post their final dose of lasmiditan.

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

Number of Subjects:

Up to 40 subjects may be enrolled in Cohort 1 in order that 30 complete the study. Up to 30 subjects may be enrolled in Cohort 2 in order that 24 complete the study. Up to 70 subjects may be enrolled in total.

Statistical analysis:

Safety parameters that will be assessed include safety lab parameters, vital signs, Colombia-Suicide Severity Rating Scale (C-SSRS) scores and electrocardiogram (ECG) parameters. The parameters will be listed, and summarized using standard descriptive statistics.

Pharmacokinetic parameter estimates for lasmiditan and its metabolites and the probe drugs will be calculated by standard noncompartmental methods of analysis. Trough concentrations of lasmiditan and its metabolites will be evaluated graphically and/or descriptively for achievement of steady-state. Pharmacokinetic parameter estimates for each probe drug will be evaluated to delineate the effects of drug interaction in Cohort 1. Probe drugs administered in the absence of lasmiditan will represent reference treatments and will be analyzed separately. Probe drugs administered with lasmiditan will represent the test treatments and will be analyzed separately. Log-transformed C_{max}, and AUC(0-∞) estimates of each probe drug will be evaluated in a linear mixed-effects analysis of variance model with a fixed effect for treatment and a random effect for subject. The treatment differences will be back-transformed to present ratios of geometric least squares means and the corresponding 90% confidence intervals (CIs).

The t_{max} of each probe drug will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CIs, and p-values from the Wilcoxon test will be calculated.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHE Cohort 1

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Informed Consent	X												
Subject Admission to CRU		X											
Subject Discharge from CRU										X			
Randomization						X							
Lasmiditan or Placebo Administration						X	X	X					
Probe Drugs Administration			X					X					
Medical History	X	X											
AEs and Medication Review		X	X	X	X	X	X	X	X	X	X	X	AE and medication review will be ongoing from Day -4
Height & Weight	X	X											Height recorded only at Screening

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Orthostatic Vital Signs	X	X				Predose, 0.5, 1, 2 h	Day 2 Predose	Predose, 0.5, 1, 2 h					Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes. Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Vital Signs (supine)	X	X	Predose 2, 4 h			Predose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2 predose	Predose, 0.5 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h			X	Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator. All vitals should be taken in triplicate apart from follow-up and screening visits where a single measurement will be taken.
Screening Laboratory Tests	X												
Clinical Lab Tests		X			X		Day 2, Day 6			X		X	See Appendix 2 for details.
HIV/Hepatitis Tests	X												

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Urine Drug Screen and Ethanol Test	X	X											
FSH Test	X												Females only to confirm menopausal status.
Pregnancy Test	X	X										X	Serum pregnancy test will be performed at all timepoints. Females of childbearing potential only.
12-lead Safety ECG	X	X			X	Predose, 1, 2, 4 h	Day 2 Predose	Predose, 1, 2, 4 h	24 h				Single ECG readings will be taken. Timepoints relative to lasmiditan dosing on Days 1 and 7.
Physical Exam	X	X		X			Day 2 Day 6	Predose		X		X	After screening, medical assessment only performed to include targeted examination, as appropriate.
Plasma PK Samples (lasmiditan)						0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2(24 h), Predose (Days 3-5)	Predose, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h				Timepoints relative to dosing on Days 1 and 7. Predose samples to be taken on Days 3, 4 and 5 for assessment of steady-state.

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Plasma PK Samples (probe)			Predose 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h	48 h			Predose , 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h	48 h			Timepoints relative to dosing on Days -3 and 7.
Exploratory Plasma Sample (Cortisol)						Predose		Predose					
Urine Sample for 2 Exploratory Analyses (lasmiditan metabolites and 6-βOHC)						X		X					0 to 24 h urine collection on Days 1 and 7 (timepoints relative to lasmiditan dosing on Day 1 and 7)
Pharmaco-genetics sample		X											
The Benzodiazepine Withdrawal Symptom Questionnaire							X	X	X	X	X	X	Questionnaire to be administered daily via phone by a member of CRU staff following discharge from the CRU on Day 9 until the follow-up visit.
Physician Withdrawal Checklist								Predose				X	
C-SSRS and Self-Harm	X	X										X	"Baseline" questionnaire to be used at screening, all

Supplement													other timepoints use "Since Last Visit" questionnaire

Abbreviations: 6 βOHC = 6-beta hydroxycortisol; AE = Adverse event; CRU = Clinical Research Unit; C-SSRS =Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discharge; FSH = follicle stimulating hormone, FU= follow-up visit; h = hours; HIV = human immunodeficiency virus; PK = pharmacokinetic.

Note: If multiple procedures take place at the same timepoint, the following order of the procedure should be: ECG, supine vital signs, orthostatic vital signs, and venipuncture. Where venipuncture and other procedures take place at the same timepoint, the following time windows for obtaining blood samples should be maintained: 0 to 2.5 hours postdose: ±5 minutes; 3 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes.

Study Schedule Protocol H8H-MC-LAHE Cohort 2

Screening		Days							FU/ED	Comments
Procedure	Days -29 to -1	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Informed Consent	X									
Subject Admission to CRU		X								
Subject Discharge from CRU							X			
Randomization			X							
Lasmiditan or Placebo Administration			X	X	X					
Medical History	X	X								
AEs and Medication review		X	X	X	X	X	X	X	X	AE and medication review will be ongoing from Day -1.
Height & weight	X	X								Height recorded only at Screening.
Vital Signs (supine)	X		Predose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2 Predose	Predose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h			X	Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator. All vitals should be in triplicate, apart from screening and follow-up visits where a single measurement will be taken.

Screening		Days							FU/ED	Comments
Procedure	Days -29 to -1	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Orthostatic Vital Signs	X	X	Predose, 0.5, 1, 2 h	Day 2 Predose	Predose, 0.5, 1, 2 h					Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes. Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Screening Laboratory Tests	X									
Clinical Lab Tests		X		Day 2, Day 6			X		X	
HIV/Hepatitis Tests	X									
Urine Drug Screen and Ethanol Test	X	X								
FSH Test	X									Females only to confirm menopausal status.
Pregnancy Test	X	X							X	Serum pregnancy test will be performed at all timepoints. Females of childbearing potential only.
12-lead Safety ECG	X	X	Predose, 1, 2, 4 h	Day 2 Predose	Predose, 1, 2, 4 h	24 h				Single ECG readings will be taken. Timepoints relative to lasmiditan dosing on Days 1 and 7.
Physical Exam	X	X		X			X		X	After screening, medical assessment only performed to include targeted examination, as appropriate.

Screening		Days							FU/ED	Comments
Procedure	Days -29 to -1	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Plasma PK Samples (lasmiditan)			0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2 (24 h), Predose (Days 3 to 5)	Predose, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h				Timepoints relative to dosing on Days 1 and 7. Predose samples to be taken on Days 3, 4 and 5 for assessment of steady-state.
Exploratory Plasma Sample (Cortisol)			Predose		Predose					
Urine Sample for 2 Exploratory Analyses (lasmiditan metabolites and 6-βOHC)			X		X					0 to 24 h urine collection on Days 1 and 7 (timepoints relative to lasmiditan dosing on Day 1 and 7)
Pharmacogenetics Sample		X								
The Benzodiazepine Withdrawal Symptom Questionnaire				X	X	X	X	X	X	Questionnaire to be administered daily via phone by a member of CRU staff following discharge from the CRU on Day 9 until the follow-up visit.
Physician Withdrawal Checklist					Predose				X	
C-SSRS and Self-Harm Supplement	X	X							X	"Baseline" questionnaire to be used at Screening , all other timepoints use "Since Last Visit" questionnaire

Abbreviations: 6-βOHC = 6-beta hydroxycortisol, AE = Adverse event; CRU = Clinical Research Unit; C-SSRS =Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discharge; FSH = follicle stimulating hormone; FU = follow-up visit; h = hours; HIV = human immunodeficiency virus; PK = pharmacokinetic.

Note: If multiple procedures take place at the same timepoint, the following order of the procedure should be: ECG, supine vital signs, orthostatic vital signs, and venipuncture. Where venipuncture and other procedures take place at the same timepoint, the following time windows for obtaining blood samples should be maintained: 0 to 2.5 hours postdose: ±5 minutes; 3 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes.

3. Introduction

3.1. Study Rationale

Lasmiditan is a small molecule 5-HT1F receptor agonist being developed for the acute treatment of migraine at doses up to 200 mg.

Triptans, which are 5-HT1B/1D receptor agonists, are well established as an acute therapy for migraine, though they are not effective in all patients. Triptans were developed as cerebral vasoconstrictors, mediated via their affinity for 5-HT1B receptors located on vascular smooth muscle. Inherent in this mechanism of action is a liability for coronary vasoconstriction, and therefore, triptans are contraindicated in patients with cardiovascular disease.

Unlike triptans, lasmiditan is a highly selective and potent agonist at the 5-HT1F receptor with >470 -fold higher affinity for the 5-HT1F receptor than for 5-HT1B/1D receptors.

Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans. Lasmiditan has been shown to be well-tolerated at single doses up to 400 mg in healthy subjects and migraine patients; however, safety, tolerability, and pharmacokinetics (PK) have not been assessed after multiple dosing at any dose level.

This study aims to evaluate the safety, tolerability, PK, and potential withdrawal symptoms following once-daily dosing of lasmiditan. Preclinical studies have indicated that lasmiditan and some of its metabolites may induce, but not inhibit, the expression and activity of cytochrome P450 (CYP) 1A2, CYP2C9, and CYP3A enzymes. Cohort 1 of the study aims to examine the effect of multiple doses of lasmiditan upon CYP1A2, CYP2C9, and CYP3A activity via concomitant administration and PK monitoring of a probe drug cocktail including caffeine (CYP1A2 substrate), tolbutamide (CYP2C9 substrate) and midazolam (CYP3A4/5 substrate). Cytochrome P450 3A induction will also be assessed in both cohorts by evaluation of concentrations of 6-beta hydroxycortisol (6-βOHC) excreted in urine relative to plasma concentrations of cortisol.

3.2. Background

Two Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine, using doses of up to 45 mg over 20 minutes of the intravenous (IV) and up to 400 mg of the oral tablet formulation. One Phase 3 randomized, double-blind, placebo-controlled trial has been completed in the United States (COL MIG-301 [SAMURAI]), where 1856 subjects were randomized to 100 mg lasmiditan (630 subjects), 200 mg lasmiditan (609 subjects), or placebo (617 subjects), respectively. In the SAMURAI study, both 100 mg and 200 mg doses of orally administered lasmiditan achieved superior 2-hour headache pain free rate and the most relief of bothersome migraine symptoms (nausea, phonophobia, and photophobia) compared to placebo.

Across the completed Phase 1, 2, and 3 clinical studies, doses of 0.1 mg to 400 mg of lasmiditan were evaluated in healthy subjects or patients with migraine. Lasmiditan has been administered to 230 healthy subjects in 5 Phase 1 studies: as IV doses ranging from 0.1 to 180 mg (H8H-BD-LACA; 40 subjects); as an oral or sublingual solution with doses ranging from 25 to

400 mg and 1 to 32 mg, respectively (COL MIG-102; 60 subjects); as an oral solution at a dose of 200 mg or as oral tablets at doses of 50 or 200 mg (COL MIG-103; 44 subjects); as oral tablets at a dose of 200 mg (COL MIG-104; 30 subjects); and as oral tablets at doses of 100 or 400 mg (COL MIG-105; 56 subjects). Two Phase 2 studies have been completed, evaluating IV doses ranging from 2.5 to 45 mg (COL MIG-201) and oral tablets ranging from 50 to 400 mg (COL MIG-202). In the Phase 3 SAMURAI (COL MIG-301) study, 1856 subjects aged 18 to 79 years received at least 1 dose of lasmiditan or placebo, with 1239 subjects receiving oral tablets of 100 or 200 mg lasmiditan.

Compared with placebo, the most frequently reported treatment-emergent adverse events (TEAEs) after receiving lasmiditan included somnolence, fatigue, dizziness, paresthesia, and hot flush. The majority of these TEAEs were mild or moderate in severity and none led to subject withdrawal. One subject experienced a serious adverse event (SAE) of dizziness that was moderate in severity (lasmiditan 200 mg, COL MIG-202)

Oral doses of lasmiditan up to 400 mg (COL MIG-103) did not demonstrate any clinically relevant changes in electrocardiograms (ECGs), including QT interval/corrected QT interval, following administration to healthy subjects. In the thorough QT study (COL MIG-105) in healthy subjects, no clinically significant changes in blood pressure, heart rate, or 12-lead ECG were observed at the 100 or 400 mg dose levels. Lasmiditan caused no significant QT prolongation at either dose.

In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1 to 2.5 hours after a single oral dose ranging from 25 to 400 mg, and the geometric mean terminal half-life was approximately 4 to 6 hours. The maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC) values following a 400 mg oral dose (COL MIG-102) were comparable to that following a 180 mg IV dose infused over 60 minutes (H8H-BD-LACA). Lasmiditan exhibited dose-linear PK; low to moderate inter-subject variability in exposure was observed across doses (% coefficient of variance) up to 61% and 45% for C_{max} and AUC, respectively [COL MIG-102]). Co-administration of lasmiditan with a high fat diet led to a delay in median time of C_{max} (t_{max}) value by approximately 1 hour and a modest (~20%) increase in lasmiditan C_{max} and AUC values, relative to that under fasted conditions. Pharmacokinetics of lasmiditan following repeated daily administration has not been previously evaluated. However, accumulation of lasmiditan is not expected, based on the short terminal half-life observed following a single oral dose.

Human metabolism has been investigated using liquid chromatography-tandem mass spectrometry (LC-MS/MS) following dosing with lasmiditan, where up to 11 metabolites were detected in plasma and urine, including 3 major metabolites (M7, M8, and M18). The relative proportions of metabolites to parent drug remained reasonably constant throughout the oral dose range studied and their PK were approximately linear. The half-life of the metabolites ranged from ~4.5 hours to ~12 hours.

3.3. Benefit/Risk Assessment

The primary objective for this study is to explore the safety and tolerability of lasmiditan after multiple oral doses at potential therapeutic dose levels. Current Phase 3 studies have allowed subjects to self-administer a repeat dose of 200 mg lasmiditan at least 2 hours after the first dose and therefore the maximum daily dose to be evaluated in this study is 400 mg. There is no anticipated therapeutic benefit for the subjects in this study.

In healthy male and female subjects single oral doses of lasmiditan up to 400 mg were not associated with drug related SAEs or study withdrawals due to adverse events (AEs). Multiple once-daily doses of 200 mg and 400 mg have not been administered previously in humans. The incidence of central nervous system AEs has been correlated with increases in dose; however the AEs observed have been transient. The probe drugs selected for use in this study are commonly used in studies of drug-drug interactions, and the planned doses are expected to be well-tolerated. Data suggests that lasmiditan is an inducer of CYP enzymes; therefore probe drug exposures are expected to decrease following exposure to lasmiditan. Dosing in this study will be conducted in an inpatient setting, and subjects will be monitored in house for at least 48 hours after the final dose of lasmiditan and/or probe drug cocktail.

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of lasmiditan are to be found in the Investigator's Brochure (IB). More information about the risks, SAEs and reasonable anticipated AEs of the probe drug cocktail are to be found in the respective package inserts and reference labels.

4. Objectives and Endpoints

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

Table LAHE.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective of this study is to explore the safety and tolerability of multiple doses of 200 mg and 400 mg lasmiditan in healthy subjects.	Incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).
Secondary • To evaluate the plasma PK of multiple doses of lasmiditan and its major metabolites.	C_{max}, t_{max}, AUC over one dosing interval (AUC_{τ}).
• To evaluate the effect of multiple doses of lasmiditan on CYP1A2, CYP2C9, and CYP3A activity.	C_{max}, T_{max}, AUC from time zero to infinity (AUC[0-∞]), and AUC from time zero to last observable concentration (AUC[0-t_{last}]) of probe drugs.
• To evaluate any potential withdrawal symptoms following once-daily dosing of lasmiditan.	Responses to the benzodiazepine withdrawal symptom questionnaire and physician withdrawal checklist.
Exploratory • To evaluate concentrations of 6-beta hydroxycortisol (6-βOHC) excreted in urine relative to plasma concentrations of cortisol as an indicator of CYP3A induction before and after treatment with 200 and 400 mg lasmiditan for 7 days.	Ratio of urinary 6-βOHC and plasma cortisol concentrations.
• To profile urine for lasmiditan metabolites after multiple doses.	

5. Study Design

5.1. Overall Design

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

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

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

Subjects will be discharged from the CRU on Day 9 at the discretion of the investigator.

Subjects in Cohort 2 will be admitted to the CRU on Day -1. Subjects will begin receiving oral doses of 400 mg lasmiditan or placebo on Day 1 (at a ratio of 1:1 lasmiditan to placebo) and will be dosed once per day until Day 7 (inclusive). Subjects will be discharged from the CRU on Day 9 at the discretion of the investigator. Serial blood samples will be taken at times listed in the Schedule of Activities up to 24 hours postdose on Days 1 and 7 for the assessment of lasmiditan PK. Blood samples will be taken predose at Days 3, 4, and 5 to assess steady-state PK of lasmiditan. The potential for withdrawal symptoms following multiple dosing of lasmiditan will be assessed by daily completion of a benzodiazepine withdrawal questionnaire (Tyrer et al. 1990) by subjects in both cohorts from Day 2 of lasmiditan or placebo dosing until 14 days following the final dose of lasmiditan or placebo. Whilst resident at the CRU, subjects will complete the questionnaire under supervision of CRU staff. Subjects will be administered the questionnaire via phone by a member of CRU staff each day following discharge from the CRU on Day 9 until the follow-up visit in both cohorts. Additionally, the potential for withdrawal symptoms will be assessed using the physician withdrawal checklist (i.e. Rickels et al. 1990, 2008) on Day 7 and at follow-up.

Subjects in each cohort will return to the CRU for a follow-up visit 14 days after the final dose of lasmiditan. Subjects will be resident at the CRU for 13 days (Cohort 1) and 10 days (Cohort 2) respectively. The planned study duration for each subject will to 55 days in Cohort 1, and 52 days in Cohort 2, including screening and follow-up visits.

5.1.1. Exploratory Assessments

The effect of lasmiditan upon CYP3A-mediated cortisol metabolism will be assessed in Cohorts 1 and 2. To this end, plasma levels of cortisol and urinary concentrations of 6-βOHC will be determined on Day 1 and Day 7. Urine samples will also be collected for future exploratory analysis, and may be used for lasmiditan metabolite identification and analysis.

5.2. Number of Participants

Up to 40 and 30 subjects may be enrolled to Cohort 1 and Cohort 2 respectively, so that 30 and 24 subjects complete the study in each cohort, respectively.

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

A subject and investigator-blinded, randomized and placebo-controlled design is being used for this study to minimize the effect of bias on the safety and tolerability objectives. Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. The benzodiazepine withdrawal symptom questionnaire (Tyrer et al. 1990) and physician withdrawal checklist (Rickels et al. 2008) will be completed to assess any potential withdrawal symptoms following repeated dosing of lasmiditan. Subjects in Cohort 1 will receive 2 single doses of midazolam, a benzodiazepine, during the study. The doses of midazolam will however be low and separated by a period of 9 days; therefore the impact on results of the benzodiazepine withdrawal symptom questionnaire is likely to be negligible.

Regulatory agencies recommend conducting clinical drug interaction studies using a drug cocktail approach where interactions with multiple CYPs are investigated (European Medicines Agency [EMA] Guideline 2012; Federal Drug Administration [FDA] 2012). The drugs should be selective for specific CYP enzyme isotypes, should not interact with each other, and should be safe when administered. Many such drug cocktails exist, with differing CYP isotype specificities: one such cocktail includes midazolam, caffeine, tolbutamide, chlorzoxazone, and debrisoquine, which has been administered in previous studies (Sharma et al. 2004). The cocktail was modified for this protocol to consist of the required probes for CYP3A (midazolam), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) to specifically target the CYP isoforms of interest. The drug cocktail will be administered on Day -3 before the initiation of lasmiditan on Day 1, and on Day 7 concurrently with dosing of lasmiditan, when steady-state concentrations of lasmiditan should be achieved. Probe drug administration will be open-label, as the PK endpoints of the study are objective.

5.5. Justification for Dose

5.5.1. Lasmiditan

To date, single doses of 400 mg lasmiditan have been well-tolerated in healthy volunteers and patients. Single and double doses, separated by 2 hours, of 100 mg and 200 mg lasmiditan were well-tolerated and effective in patients enrolled in the Phase 3 SAMURAI study. In preclinical toxicology studies absorption was similar between the first and final doses in a variety of preclinical species. A dose dependent and linear increase in exposure of lasmiditan was observed in animal and human studies at dose levels similar to those planned in this study. Once-daily dosing up to 400 mg for 7 days is expected to achieve steady state, and provide sufficient exposure to lasmiditan to evaluate potential CYP induction. Dosing in Cohort 2 of the study will only occur after careful review of the safety data from subjects in Cohort 1 (including data from the follow-up visit).

5.5.2. Probe Drug Cocktail

The doses used in the drug cocktail (100 mg caffeine, 500 mg tolbutamide and 2 mg midazolam) are clinically relevant doses considered safe to administer and have been used concomitantly in previous drug cocktail clinical studies.

The rationale for the drug-drug interaction arm of the study is that lasmiditan may induce the expression of CYP enzymes in humans. It is therefore likely that if lasmiditan affects CYP expression the systemic exposure to the probe drug cocktail will be reduced due to increased drug clearance.

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.

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

Screening may occur up 28 days prior to Day -4 in Cohort 1, and 28 days prior to Day -1 in Cohort 2. Subjects who are not enrolled 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 and admission to the study:

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

[1a] male subjects will not be subject to any specific contraception requirements.

[1b] female subjects:

of childbearing potential, must test negative for pregnancy at screening, and agree to use a reliable method of birth control during the study and for 1 week following the final dose of lasmiditan. Reliable methods of contraception for female subjects of childbearing potential include the use of stable oral, implanted, or injected contraceptive hormones, bilateral tubal ligation, intrauterine device, or diaphragm with spermicide along with male partner's use of male condom with spermicide.

of non-child-bearing potential, i.e. postmenopausal or permanently sterile following hysterectomy, bilateral salpingectomy or confirmed tubal occlusion (not tubal ligation), as determined by medical history. Postmenopausal is defined as spontaneous amenorrhea for at least 12 months, and a serum follicle stimulating hormone (FSH) level greater than 40 mIU/mL, unless the subject is taking hormone replacement therapy.

[2] Subjects must be aged 18 to 65 years, inclusive at the time of screening.

[3] have a body mass index (BMI) of 19 to 35 kg/m^2, inclusive at the time of screening.

[4] have clinical laboratory test results within normal reference range for the population or investigative site, or results within 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 reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[7] have given written informed consent approved by Lilly and the ethical review board (ERB) governing the site.

6.2. Exclusion Criteria

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

[8] 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, whether biological or legally adopted.

[9] are Lilly employees or Covance employees.

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

[11] have participated, within the last 30 days in a clinical study involving an IP.

[12] have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received lasmiditan.

[13] have known allergies to lasmiditan, midazolam, caffeine, tolbutamide, related compounds, or any components of the formulations used.

[14] have a clinically significant abnormality in the 12-lead ECG, including corrected QT (QTc) interval with Fridericia's correction (QTcF) >450 msec for men or >470 msec for women or any abnormality that in the opinion of the investigator increases the risk of participating in the study (not limited to significant bradycardia or heart block).

[15] any history of prolonged QT interval, family history of QT interval prolongation or sudden death, or history of unexplained loss of consciousness.

[16] have significant history of or current cardiovascular disorders including any history of clinically significant arrhythmia, 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 study drug, or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable.

[17] In the opinion of the investigator, has history of syncope, presyncopy, vertigo, postural dizziness, or at risk for falls.

[18] have current or history of orthostatic hypotension (>20mmHg drop in systolic blood pressure, or >10mmHg drop in diastolic blood pressure) with or without dizziness and/or syncope at screening or admission to the CRU upon repeat testing.

[19] history of, show evidence of, or are undergoing treatment for significant active neuropsychiatric disease (for example, manic depressive illness, schizophrenia, depression), have a recent history of a suicide attempt (30 days within screening visit and any time between screening visit and baseline); or are clinically judged by the investigator to be at risk for suicide.

[20] show a history of CNS conditions such as strokes, transient ischemic attacks, significant head trauma, CNS infections, migraines, brain surgery or any other neurological conditions that, in the opinion of the investigator, increases the risk of participating in the study.

[21] history of hypoglycemia.

[22] known history of glucose-6-phosphate dehydrogenase deficiency.

[23] have an estimated glomerular filtration rate (eGFR) of < 60 mL/min (as measured by the CKD-EPI equation).

[24] are taking a concomitant medication or a dietary substance that affects CYP1A2, CYP2C9, and/or CYP3A isotypes within 14 days of screening.

[25] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.

[26] show evidence of hepatitis C and/or positive hepatitis C antibody.

[27] show evidence of hepatitis B and/or positive hepatitis B surface antigen.

[28] are women with a positive pregnancy test or women who are lactating.

[29] intend to use over-the-counter or prescription medication within 14 days prior to dosing of lasmiditan.

[30] have donated a blood or plasma volume of more than 500 mL within 1 month prior to the screening visit.

[31] have an average weekly alcohol intake that exceeds 21 units per week (males) or 14 units per week (females), or are unwilling to stop alcohol consumption 48 hours prior to admission and throughout the duration of the study (1 unit = 12 oz. or 360 mL of beer; 5 oz. or 150 mL of wine; 1.5 oz. or 45 mL of distilled spirits).

[32] currently use, or have a history of drug or alcohol abuse within the past 2 years.

[33] have a clinically significant abnormality in the neurological examination.

[34] are current smokers.

[35] drink more than 5 caffeinated drinks/per day, and are unwilling /unable to abstain from caffeine or xanthine containing products from 72 hours prior to admission to the end of the study.

[36] 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

Lasmiditan, placebo and probe drugs will be administered after an overnight fast of at least 10 hours. Subjects will abstain from water 1 hour before and after dosing (except for water given with the dose). Subjects will remain fasting for 3 hours postdose on Days 1 and 7 (and Day -3 in Cohort 1) at which time a meal will be served. On Days 2 to 6 in both cohorts, a light breakfast will be allowed 1 hour postdose.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine – Subjects will refrain from consuming xanthine- or caffeine-containing food and drinks from 72 hours prior to admission until the end of the study period.

Alcohol – Subjects will not consume alcohol for 48 hours prior to admission and for the duration of the study.

Tobacco – Subjects will be non-smokers and thus cannot smoke throughout the study.

6.3.3. Activity

No strenuous exercise will be allowed for 48 hours prior to admission until after the follow-up visit.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

Subjects in Cohort 1will be administered 200 mg lasmiditan (1 x 200 mg film-coated tablet) or placebo on Days 1 through 7, following an overnight fast. Subjects in Cohort 1will also receive a probe drug cocktail on Day -3 and Day 7 of the treatment period. The drug cocktail will consist of:

- a 100 mg oral dose of caffeine (as caffeine base) in tablet form
- a 500 mg oral dose of tolbutamide in tablet form
- a 2 mg dose of midazolam oral syrup.

The study site will obtain the cocktail drugs. Administration of each cocktail drug will be according to the respective instructions for use. Cocktail drugs will be administered on Day -3 with approximately 240 mL of room-temperature water to the subject in a sitting position. On Day 7, lasmiditan and probe drugs will be administered orally with 240 mL of room-temperature water. On all other dosing days, lasmiditan will be administered orally with 240 mL of room-temperature water. Additional water may be given on an individual basis if needed and amount will be recorded.

Subjects in Cohort 2 will be administered 400 mg lasmiditan (as 2 x 200 mg film-coated tablets) or placebo on Days 1 through 7, following an overnight fast. Tablets of lasmiditan or placebo will be administered orally with approximately 240 mL of room-temperature water. Additional water may be given on an individual basis if needed and amount will be recorded.

All doses in both cohorts will be given in the morning of each day, whilst in a sitting position. Subjects will not be allowed to lie supine for approximately 2 hours after dosing, unless clinically indicated, or for study procedures.

The investigator or designee is responsible for:

- explaining the correct use of the IP(s) and other study treatments to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- and returning all unused medication 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 tablet of lasmiditan contains 200 mg of active ingredient and is provided as bulk supply in bottles. Placebo tablets look identical but contain no active ingredient and will be provided in similar bulk bottles.

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

7.2. Method of Treatment Assignment

Subjects will be randomized to lasmiditan or placebo treatment using a computer generated allocation schedule.

7.2.1. Selection and Timing of Doses

Subjects in Cohort 1 and 2 will receive oral doses of 200 mg or 400 mg of lasmiditan or placebo respectively, once-daily for 7 days. Subjects in Cohort 1will receive single oral doses of the probe drug cocktail on Day -3, and Day 7 of the study period relative to lasmiditan administration. On Day 7, probe drugs will be administered concurrently with lasmiditan. The actual time of all dose administrations will be recorded in the subject's clinical report form (CRF).

7.3. Blinding

The study will be subject- and investigator-blind for lasmiditan. The investigator, site staff (apart from unblinded pharmacy staff) and subjects will be blinded to the administration of lasmiditan or placebo in Cohorts 1 and 2. Administration of the probe drugs will be open-label, as the PK endpoints in the study are considered objective.

Emergency codes will be available to the investigator. A code, which reveals the treatment 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 the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician 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

Dose modification for individual subjects will not be allowed during the study.

7.4.1. Dose Decision

Safety and tolerability data collected from Cohort 1 of the study will be assessed prior to lasmiditan administration in Cohort 2. No decision can occur without prior discussion and agreement between the investigator and the Lilly clinical pharmacologist/clinical research physician or designee.

Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to lasmiditan or the probe drug cocktail unless there is clear evidence that the event is not related. Safety data from at least 18 subjects in Cohort 1 will be required prior to the dose decision for Cohort 2. After review of these data, an agreement on whether to dose Cohort 2 will be made by the investigator and sponsor. If escalation to 400 mg is not deemed appropriate for Cohort 2 an intermediate dose of 300 mg may be considered. In the case of disagreement, the decision of the investigator will be followed, except in a situation where Lilly's proposal is the more conservative action (for example, where the investigator wishes to escalate and the Lilly clinical pharmacologist/clinical research physician does not) in which case, the Lilly proposal will be followed.

If any of the following scenarios occur in Cohort 1, dosing in Cohort 2 will be halted or delayed until thorough review by the investigator, sponsor representative, and medical consultants as appropriate. Pharmacokinetic data may also be requested and considered in dose decision:

1) a single subject experiences a SAE that is related to lasmiditan administration

2) 2 or more subjects show QTcF >500 msec or increases of QTcF values of >60 msec above the QTcF baseline value, sustained for two consecutive timepoints. The QTcF baseline value is defined as the Day 1 predose ECG of the corresponding period. If a subject shows QTcF >500 msec or increases of QTcF values of >60 msec above the QTcF baseline value, two additional ECGs will be obtained within 10 minutes and the 3 ECGs will be averaged to see if the QTcF>500 or increases of QTcF values are >60 msec above the QTcF baseline value.

3) if a suicide-related thought or behavior is identified at any time during the study or if during the study a subject gives the following responses after lasmiditan exposure:

   - a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS;
   - a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS
   - a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm all IP was received in good condition, and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive IP or study materials, and only authorized site staff may supply or administer IP. All IP 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 IP will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Concomitant medications are to be avoided during the study unless required to treat an AE or for the treatment of an ongoing medical problem.

Up to 2 grams of acetaminophen may be allowed per 24 hour period at the investigator's discretion.

If the need for any other concomitant medication arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist, clinical research physician (CRP), or designee. Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

This section is not applicable to this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

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

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a subject meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT (alanine aminotransferase) AST (aspartate aminotransferase) >5X ULN (upper limit of normal)
- ALT or AST >3X ULN sustained for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or INR >1.5 orALT or AST >3X ULN
- the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP (alkaline phosphatase) >3X ULN
- ALP>2.5X ULN and TBL >2X ULN
- ALP>2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

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, the subject must be discontinued from the study.

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 Decision
    - the investigator decides that the subject should be discontinued from the study
- Subject Decision
    - the subject, or their legal representative, requests to be withdrawn from the study.

- If a suicide-related thought or behavior is identified at any time during the study, or if during the study a subject gives:
    - A "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SRSS; or
    - A "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS
    - A "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS.
- A subject shows QTcF >500 msec or increases of QTcF values of >60 msec above the QTcF baseline value, sustained across two consecutive timepoints. The QTcF baseline value is defined as the Day 1 predose ECG of the corresponding period. If a subject shows QTcF >500 msec or increases of QTcF values of >60 msec above the QTcF baseline value, two additional ECGs will be obtained within 10 minutes and the 3 ECGs will be averaged to see if the QTcF>500 or increases of QTcF values are >60 msec above the QTcF baseline value.

In addition, a subject will also be evaluated for discontinuation if they have self-injurious behavior that would be classified as non-suicidal self-injurious behavior. It is recommended that a subject be assessed by a psychiatrist or appropriately trained professional to assist the investigator in deciding whether the subject should be discontinued from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or 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 clinical 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 health care 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 ICF is signed, study site personnel will record, via CRF, 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 IP, study procedure and the AE.

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 IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF.

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/CP, or their 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 IP) does not meet the definition of an adverse event. 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 IP 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 IP so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of lasmiditan is considered any dose higher than the planned study dose. There is no specific antidote for lasmiditan. In the event of overdose, the subject should receive appropriate supportive care and AEs should be documented.

No drug interaction studies in humans have yet been performed with lasmiditan. In the event of probe drug overdose, the package inserts should be referred to for further information on antidotes or supportive care.

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).

9.4.2. Vital Signs

For each subject, vital signs 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. All supine blood pressure and pulse rate except for screening and follow-up will be done in triplicates at approximately 1 minute intervals. The last triplicate vital sign can be used as the supine vital sign for the calculation of orthostatic changes.

Where orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for 2 minutes and no more than 3 minutes.

If the subject feels unable to stand, supine vital signs only will be recorded.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

9.4.3. 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 IP, should be reported to Lilly, or its designee, as an AE via eCRF.

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities. 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. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (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/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.

9.4.4. Colombia-Suicide Severity Rating Scale

Any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2) using the C-SSRS. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience.

Adverse event collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS, but was not captured during AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation from study treatment, this is an exception where the SAE and/or AE leading to discontinuation from study treatment should be included on the AE form and the process for reporting SAEs should be followed.

Terms captured by the use of the C-SSRS can be mapped to the Columbia Classification Algorithm of Suicide Assessment (Posner et al. 2007) to facilitate future pooling of data.

The first time the scale is administered in this study, the C-SSRS "Baseline" version will be used, and the findings will constitute the baseline assessment. The C-SSRS "Since Last Visit" scale will be used for all subsequent assessments. If a suicide-related thought or behavior is identified at any time during the study (including follow-up), a thorough evaluation will be performed by a study physician, and appropriate medical care will be provided. It is recommended that a subject be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the subject should be discontinued from study treatment. A subject does not necessarily have to be discontinued if they have self-injurious behavior that would be

classified as non-suicidal self-injurious behavior. If this situation arises, the subject will be referred to a psychiatrist or appropriately trained professional.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If, based on administration of the C-SSRS, it is determined that suicide-related behaviors have occurred, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.4.5. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs

9.4.5.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated total bilirubin ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, 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 two or more consecutive blood tests
- elevated 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

9.5.1. Lasmiditan

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan and its major metabolites (M7, M8, and M18). A maximum of 3 samples may be collected at

additional timepoints 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.

9.5.2. Probe Drug Cocktail

At the visits and times specified in the Schedule of Activities for Cohort 1, 2 venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of caffeine, tolbutamide, and midazolam. 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.

9.5.3. Bioanalysis

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

Plasma concentrations of lasmiditan and its major metabolites will be assayed using a validated LC-MS/MS method. Plasma concentrations of each analyte in the drug cocktail (caffeine, tolbutamide, and midazolam) will be assayed using respective validated LC-MS/MS methods.

Plasma remaining after the analyses may be used for exploratory work to further understand the disposition and metabolism of lasmiditan or the probe substrates.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 2 years following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses.

9.6. Pharmacodynamics

The benzodiazepine withdrawal symptom questionnaire (Tyrer et al. 1990) will be completed daily by subjects from Day 2 of lasmiditan or placebo dosing until 14 days following the final dose of lasmiditan or placebo. Whilst resident at the CRU, subjects will be administered the questionnaire by CRU staff. Subjects will be administered the questionnaire via phone by a member of CRU staff each day following discharge from the CRU on Day 9 until the follow-up visit in both cohorts. The physician withdrawal checklist (Rickels et al. 2008) will be completed by qualified CRU staff predose on Day 7 and follow-up.

9.7. Exploratory Assessments

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 2 mL each will be collected for the determination of plasma concentrations of cortisol. 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.

Beginning from the time of lasmiditan dosing on Days 1 and 7 of Cohort 1 and Cohort 2, 24-hour urine samples will be collected. The actual volume of urine collected and the time of each collection will be recorded.

One urine aliquot from the 24-hour urine collections will be taken to determine urinary concentrations of 6-βOHC.

A second urine aliquot from the 24-hour urine collections will be used for exploratory metabolite profiling.

The urine aliquot(s) will be stored for up to a maximum of 2 years after last subject visit for the study at a facility selected by the sponsor. During this time, samples remaining after the bioanalyses may be used for other exploratory analyses.

9.7.1. Bioanalysis

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

Plasma concentrations of cortisol will be determined using a validated LC-MS/MS method.

Urine concentrations of 6-βOHC concentrations will be determined using a validated LC-MS/MS method.

9.8. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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 response to lasmiditan and to investigate genetic variants thought to play a role in migraine. 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 ERBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. 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 technology utilized, data generated will be used only for the specific research scope described in this section.

9.9. Biomarkers

This section is not applicable for this study.

9.10. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

10.1.1. Cohort 1

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

10.1.1.1. Caffeine

For caffeine AUC the intrasubject CV was estimated to be 21.0% (Blanchard and Sawers 1983). Based on this assumption, 21 subjects will provide a precision (i.e. half-width of the 90% confidence interval) of 0.13 on the log scale, with 90% power, which corresponds to 12.4% on the natural scale. For caffeine C_{max} the intrasubject CV was estimated to be 23.4% (Turpault et al. 2009). Based on this assumption, 21 subjects will provide a precision of 0.15 on the log scale, with 90% power, which corresponds to 13.7% on the natural scale.

10.1.1.2. Midazolam

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

10.1.1.3. Tolbutamide

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

10.1.1.4. Benzodiazepine Withdrawal Symptom Questionnaire

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

10.1.2. Cohort 2

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

10.2. Populations for 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 subjects' age, sex, weight, height, BMI, race, and other demographic characteristics will be recorded and summarized using descriptive statistics.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacokinetic analyses will be conducted on the full analysis set. For drug cocktail PK, the full analysis set includes all data from all subjects receiving at least one dose of drug cocktail with evaluable PK data, according to the treatment the subjects actually received. For lasmiditan PK, the full analysis set includes all data from all subjects receiving at least one dose of lasmiditan with evaluable PK data.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements. Baseline for safety analyses will be the predose measurement on Day 1.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with IP and/or with probe drug as perceived by the investigator. Symptoms reported to occur

prior to enrollment 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 regulatory dictionary.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety lab parameters, vital signs, ECG parameters, and C-SRSS scores. The parameters will be listed, and summarized using standard descriptive statistics.

To assess the impact of lasmiditan on pulse rate, descriptive statistics such as the mean, median, and standard deviation will be calculated for each timepoint by dose level. Summary statistics for baseline-corrected pulse rates will also be calculated and presented. The corresponding box plots for the pulse rate and baseline-corrected heart rate will be presented as well.

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan and its major metabolites as well as caffeine, midazolam, and tolbutamide will be calculated by standard noncompartmental methods of analysis and will be listed and summarized for each group of subjects using descriptive statistics.

The primary parameters for analysis will be C_{max}, AUC(0-∞), AUC(0-t_{last}) and t_{max} of midazolam, tolbutamide, and caffeine. Additionally, C_{max}, t_{max}, and AUC_{τ} will be reported for plasma concentrations of lasmiditan, and metabolites (M7, M8, and M18). Other noncompartmental parameters, such as half-life, apparent clearance, apparent volume of distribution, metabolite ratio, and accumulation ratio may be reported. AUC(0-t_{last}) and AUC(0-∞) may be assessed for lasmiditan and its metabolites to determine temporal linearity.

10.3.2.2. Pharmacokinetic Statistical Inference

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

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

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

analyzed using the same method described above. The t_{max} will be analyzed using a Wilcoxon signed rank test. Estimates of the median difference based on the observed medians, 90% CI, and p-values from the Wilcoxon test will be calculated.

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

10.3.3. Pharmacodynamic Evaluations

10.3.3.1. Pharmacodynamic Parameter Estimation

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

10.3.3.2. Pharmacodynamic Statistical Inference

Benzodiazepine withdrawal symptom questionnaire scores and physician withdrawal checklist will be listed, and summarized using standard descriptive statistics. Total score at each time point will be averaged for each treatment group in each cohort based upon the available data, and the lasmiditan group will be compared with the placebo group via t-test at each time point within each cohort.

10.3.4. Exploratory Assessment Evaluations

10.3.4.1. Exploratory Parameter Estimation

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

10.3.4.2. Exploratory Parameter Statistical Inference

Exploratory parameters may be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.5. Data Review During the Study

Interim access to the data is scheduled to occur after Cohort 1 as described in Section 7.4.1. The purpose of this interim review is to review the safety data and determine the dose for the next cohort. The investigator and the Lilly study team will make the determination regarding dose escalation based upon their review of the safety and tolerability data. The investigator will remain blinded and the Lilly study team may be unblinded during this interim review. If available, summary PK data may also be reviewed, but is not required for selecting the Cohort 2 dose level.

10.4. 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.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
6-βOHC	6-β-hydroxycortisol
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
AUC_τ	area under the concentration versus time curve over one dosing interval
$AUC(0\text{-}\infty)$	area under the concentration versus time curve from zero to infinity
$AUC(0\text{-}t_{last})$	area under the concentration versus time curve from time zero to time t, where t is the last timepoint with a measurable concentration
blinding	A procedure in which one 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 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/his 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.
BMI	body mass index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNS	central nervous system
CV	coefficient of variance
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or 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 confirm 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 timepoint, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
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
CYP	cytochrome P450
eCRF	electronic case report form
ED	early discharge
eGFR	estimated glomerular filtration rate as measured by the CKD-EPI equation
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.
EMA	European Medicines Agency
ERB	ethical review board
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
FU	follow-up visit
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization

IND	Investigational New Drug: An application to the FDA to allow testing of a new drug in humans.
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product (IP)	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.
IV	intravenous
LC-MS/MS	liquid chromatography-tandem mass spectrometry
Legal Representative	An individual or 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.
MTD	maximum tolerated dose
randomize	the process of assigning subjects/patients to an experimental group on a random basis
PK	pharmacokinetic
QTc	corrected QT interval
QTcF	QT interval with Friederica's correction
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
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 to maximum drug concentration

ULN	upper limit of normal
WBC	white blood cell

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Total CO_2
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Magnesium
Platelets	Glucose (fasting)
Differential WBC absolute counts and % of:	Blood urea nitrogen (BUN)
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase (ALP)
Basophils	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
Urinalysis	Creatinine
	eGFR
Microscopic	
Specific gravity	
pH	
Protein	
Glucose	Urine drug and ethanol screen
Ketones	Hepatitis B surface antigen[a]
Bilirubin	Hepatitis C antibody[a]
Urobilinogen	HIV[a]
Blood	Pregnancy test
Nitrite	FSH [a]

Abbreviations: eGFR= estimated glomerular filtration rate, assessed by CKD-EPI equation; FSH = follicle stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

[a] Performed at screening only, as applicable

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.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by 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.

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/patient personal information collected will be provided in a written document to the subject/patient 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 CRP.

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 antibody)[a]**
CPK	

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

[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-LAHE Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples (Cohort 1/Cohort 2)	Total Volume (mL) (Cohort 1/Cohort 2)
Screening tests[a]	19.5	1/1	19.5/19.5
Clinical laboratory tests[a]	12.5	6/5	75/62.5
Serum pregnancy test	5	3/3	15/15
Exploratory cortisol assessment	2	2/2	4/4
Lasmiditan pharmacokinetics	2	29/29	58/58
Probe drug pharmacokinetics	2 x 2	26/NA	104/NA
Pharmacogenetics	10	1/1	10/10
Total			285.5/169
Total for clinical purposes rounded up to nearest 10 mL			290/170

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

Appendix 6. Protocol Amendment H8H-MC-LAHE(b) Summary: Multiple-Ascending Dose, Safety, Tolerability, Pharmacokinetic, and Drug-Drug Interaction Study of Lasmiditan

Overview

Protocol H8H-MC-LAHE, Multiple-Ascending Dose, Safety, Tolerability, Pharmacokinetic, and Drug-Drug Interaction Study of Lasmiditan, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall change and rationale made to this protocol are to comply with FDA feedback received via email on 24 August 2017. Details of the change are as follows:

- Physician Withdrawal Checklist will be administered on Day 7 and at follow-up to further assess the potential symptoms of withdrawal.

Revised Protocol Sections

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

1. Protocol Synopsis

Title of Study:

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

Objective(s)/Endpoints:

Objectives	Endpoints
Primary The primary objective of this study is to explore the safety and tolerability of multiple doses of 200 mg and 400 mg lasmiditan in healthy subjects.	Incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).
Secondary • To evaluate the plasma pharmacokinetics (PK) of multiple doses of lasmiditan and its major metabolites.	Maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), area under the concentration versus time curve (AUC) over one dosing interval (AUC_τ).
• To evaluate the effect of multiple doses of lasmiditan on CYP1A2, CYP2C9, and CYP3A activity.	C_{max}, T_{max}, AUC from time zero to infinity (0-∞), and AUC from time zero to last observable concentration AUC(0-t_{last}) of probe drugs.
• To evaluate any potential withdrawal symptoms following once-daily dosing of lasmiditan.	Responses to the benzodiazepine withdrawal symptom questionnaire and physician withdrawal checklist.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHE Cohort 1

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Informed Consent	X												
Subject Admission to CRU		X											
Subject Discharge from CRU										X			
Randomization						X							
Lasmiditan or Placebo Administration						X	X	X					
Probe Drugs Administration			X					X					
Medical History	X	X											
AEs and Medication Review		X	X	X	X	X	X	X	X	X	X	X	AE and medication review will be ongoing from Day -4
Height & Weight	X	X											Height recorded only at Screening

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Orthostatic Vital Signs	X	X				Predose, 0.5, 1, 2 h	Day 2 Predose	Predose, 0.5, 1, 2 h					Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes. Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Vital Signs (supine)	X	X	Predose 2, 4 h			Predose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2 predose	Predose, 0.5 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h			X	Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator. All vitals should be taken in triplicate apart from follow-up and screening visits where a single measurement will be taken.
Screening Laboratory Tests	X												
Clinical Lab Tests		X			X		Day 2, Day 6			X		X	See Appendix 2 for details.
HIV/Hepatitis Tests	X												

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Urine Drug Screen and Ethanol Test	X	X											
FSH Test	X												Females only to confirm menopausal status.
Pregnancy Test	X	X										X	Serum pregnancy test will be performed at all timepoints. Females of childbearing potential only.
12-lead Safety ECG	X	X			X	Predose, 1, 2, 4 h	Day 2 Predose	Predose, 1, 2, 4 h	24 h				Single ECG readings will be taken. Timepoints relative to lasmiditan dosing on Days 1 and 7.
Physical Exam	X	X		X			Day 2 Day 6	Predose		X		X	After screening, medical assessment only performed to include targeted examination, as appropriate.
Plasma PK Samples (lasmiditan)						0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2(24 h), Predose (Days 3-5)	Predose, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h				Timepoints relative to dosing on Days 1 and 7. Predose samples to be taken on Days 3, 4 and 5 for assessment of steady-state.

Screening		Days										FU/ED	Comments
Procedure	Days -32 to -4	-4	-3	-2	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Plasma PK Samples (probe)			Predose 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h	48 h			Predose , 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h	48 h			Timepoints relative to dosing on Days -3 and 7.
Exploratory Plasma Sample (Cortisol)						Predose		Predose					
Urine Sample for 2 Exploratory Analyses (lasmiditan metabolites and 6-βOHC)						X		X					0 to 24 h urine collection on Days 1 and 7 (timepoints relative to lasmiditan dosing on Day 1 and 7)
Pharmaco-genetics sample		X											
The Benzodiazepine Withdrawal Symptom Questionnaire							X	X	X	X	X	X	Questionnaire to be administered daily via phone by a member of CRU staff following discharge from the CRU on Day 9 until the follow-up visit.
Physician Withdrawal Checklist								Predose				X	
C-SSRS and Self-Harm	X	X										X	"Baseline" questionnaire to be used at screening, all

Supplement													other timepoints use "Since Last Visit" questionnaire

Abbreviations: 6 βOHC = 6-beta hydroxycortisol; AE = Adverse event; CRU = Clinical Research Unit; C-SSRS =Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discharge; FSH = follicle stimulating hormone, FU= follow-up visit; h = hours; HIV = human immunodeficiency virus; PK = pharmacokinetic.

Note: If multiple procedures take place at the same timepoint, the following order of the procedure should be: ECG, supine vital signs, orthostatic vital signs, and venipuncture. Where venipuncture and other procedures take place at the same timepoint, the following time windows for obtaining blood samples should be maintained: 0 to 2.5 hours postdose: ±5 minutes; 3 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes.

Study Schedule Protocol H8H-MC-LAHE Cohort 2

Screening		Days							FU/ED	Comments
Procedure	Days -29 to -1	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Informed Consent	X									
Subject Admission to CRU		X								
Subject Discharge from CRU							X			
Randomization			X							
Lasmiditan or Placebo Administration			X	X	X					
Medical History	X	X								
AEs and Medication review		X	X	X	X	X	X	X	X	AE and medication review will be ongoing from Day -1.
Height & weight	X	X								Height recorded only at Screening.
Vital Signs (supine)	X		Predose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2 Predose	Predose, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h			X	Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator. All vitals should be in triplicate, apart from screening and follow-up visits where a single measurement will be taken.

Screening		Days							FU/ED	Comments
Procedure	Days -29 to -1	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Orthostatic Vital Signs	X	X	Predose, 0.5, 1, 2 h	Day 2 Predose	Predose, 0.5, 1, 2 h					Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes. Timepoints may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Screening Laboratory Tests	X									
Clinical Lab Tests		X		Day 2, Day 6			X		X	
HIV/Hepatitis Tests	X									
Urine Drug Screen and Ethanol Test	X	X								
FSH Test	X									Females only to confirm menopausal status.
Pregnancy Test	X	X							X	Serum pregnancy test will be performed at all timepoints. Females of childbearing potential only.
12-lead Safety ECG	X	X	Predose, 1, 2, 4 h	Day 2 Predose	Predose, 1, 2, 4 h	24 h				Single ECG readings will be taken. Timepoints relative to lasmiditan dosing on Days 1 and 7.
Physical Exam	X	X		X			X		X	After screening, medical assessment only performed to include targeted examination, as appropriate.

Screening		Days							FU/ED	Comments
Procedure	Days -29 to -1	-1	1	2 to 6	7	8	9	10 to FU		FU approximately 14 days post final dose
Plasma PK Samples (lasmiditan)			0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	Day 2 (24 h), Predose (Days 3 to 5)	Predose, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h				Timepoints relative to dosing on Days 1 and 7. Predose samples to be taken on Days 3, 4 and 5 for assessment of steady-state.
Exploratory Plasma Sample (Cortisol)			Predose		Predose					
Urine Sample for 2 Exploratory Analyses (lasmiditan metabolites and 6-βOHC)			X		X					0 to 24 h urine collection on Days 1 and 7 (timepoints relative to lasmiditan dosing on Day 1 and 7)
Pharmacogenetics Sample		X								
The Benzodiazepine Withdrawal Symptom Questionnaire				X	X	X	X	X	X	Questionnaire to be administered daily via phone by a member of CRU staff following discharge from the CRU on Day 9 until the follow-up visit.
Physician Withdrawal Checklist					Predose				X	
C-SSRS and Self-Harm Supplement	X	X							X	"Baseline" questionnaire to be used at Screening , all other timepoints use "Since Last Visit" questionnaire

Abbreviations: 6-βOHC = 6-beta hydroxycortisol, AE = Adverse event; CRU = Clinical Research Unit; C-SSRS =Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discharge; FSH = follicle stimulating hormone; FU = follow-up visit; h = hours; HIV = human immunodeficiency virus; PK = pharmacokinetic.

Note: If multiple procedures take place at the same timepoint, the following order of the procedure should be: ECG, supine vital signs, orthostatic vital signs, and venipuncture. Where venipuncture and other procedures take place at the same timepoint, the following time windows for obtaining blood samples should be maintained: 0 to 2.5 hours postdose: ±5 minutes; 3 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes.

4. Objectives and Endpoints

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

Table LAHE.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective of this study is to explore the safety and tolerability of multiple doses of 200 mg and 400 mg lasmiditan in healthy subjects.	Incidence of serious adverse events (SAEs) and treatment-emergent adverse events (TEAEs).
Secondary • To evaluate the plasma PK of multiple doses of lasmiditan and its major metabolites.	C_{max}, t_{max}, AUC over one dosing interval (AUC_{τ}).
• To evaluate the effect of multiple doses of lasmiditan on CYP1A2, CYP2C9, and CYP3A activity.	C_{max}, T_{max}, AUC from time zero to infinity (AUC[0-∞]), and AUC from time zero to last observable concentration (AUC[0-t_{last}]) of probe drugs.
• To evaluate any potential withdrawal symptoms following once-daily dosing of lasmiditan.	Responses to the benzodiazepine withdrawal symptom questionnaire and physician withdrawal checklist.
Exploratory • To evaluate concentrations of 6-beta hydroxycortisol (6-βOHC) excreted in urine relative to plasma concentrations of cortisol as an indicator of CYP3A induction before and after treatment with 200 and 400 mg lasmiditan for 7 days.	Ratio of urinary 6-βOHC and plasma cortisol concentrations.
• To profile urine for lasmiditan metabolites after multiple doses.	

5. Study Design

5.1. Overall Design

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

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

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

Subjects will be discharged from the CRU on Day 9 at the discretion of the investigator.

Subjects in Cohort 2 will be admitted to the CRU on Day -1. Subjects will begin receiving oral doses of 400 mg lasmiditan or placebo on Day 1 (at a ratio of 1:1 lasmiditan to placebo) and will be dosed once per day until Day 7 (inclusive). Subjects will be discharged from the CRU on Day 9 at the discretion of the investigator. Serial blood samples will be taken at times listed in the Schedule of Activities up to 24 hours postdose on Days 1 and 7 for the assessment of lasmiditan PK. Blood samples will be taken predose at Days 3, 4, and 5 to assess steady-state PK of lasmiditan. The potential for withdrawal symptoms following multiple dosing of lasmiditan will be assessed by daily completion of a benzodiazepine withdrawal questionnaire (Tyrer et al. 1990) by subjects in both cohorts from Day 2 of lasmiditan or placebo dosing until 14 days following the final dose of lasmiditan or placebo. Whilst resident at the CRU, subjects will complete the questionnaire under supervision of CRU staff. Subjects will be administered the questionnaire via phone by a member of CRU staff each day following discharge from the CRU on Day 9 until the follow-up visit in both cohorts. Additionally, the potential for withdrawal symptoms will be assessed using the physician withdrawal checklist (i.e. Rickels et al. 1990, 2008) on Day 7 and at follow-up.

Subjects in each cohort will return to the CRU for a follow-up visit 14 days after the final dose of lasmiditan. Subjects will be resident at the CRU for 13 days (Cohort 1) and 10 days (Cohort 2) respectively. The planned study duration for each subject will to 55 days in Cohort 1, and 52 days in Cohort 2, including screening and follow-up visits.

5.4. Scientific Rationale for Study Design

A subject and investigator-blinded, randomized and placebo-controlled design is being used for this study to minimize the effect of bias on the safety and tolerability objectives. Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications. The benzodiazepine withdrawal symptom questionnaire (Tyrer et al. 1990) and physician withdrawal checklist (Rickels et al. 2008) will be completed ~~by subjects~~ to assess any potential withdrawal symptoms following repeated dosing of lasmiditan. Subjects in Cohort 1 will receive 2 single doses of midazolam, a benzodiazepine, during the study. The doses of midazolam will however be low and separated by a period of 9 days; therefore the

impact on results of the benzodiazepine withdrawal symptom questionnaire is likely to be negligible.

Regulatory agencies recommend conducting clinical drug interaction studies using a drug cocktail approach where interactions with multiple CYPs are investigated (European Medicines Agency [EMA] Guideline 2012; Federal Drug Administration [FDA] 2012). The drugs should be selective for specific CYP enzyme isotypes, should not interact with each other, and should be safe when administered. Many such drug cocktails exist, with differing CYP isotype specificities: one such cocktail includes midazolam, caffeine, tolbutamide, chlorzoxazone, and debrisoquine, which has been administered in previous studies (Sharma et al. 2004). The cocktail was modified for this protocol to consist of the required probes for CYP3A (midazolam), CYP1A2 (caffeine), and CYP2C9 (tolbutamide) to specifically target the CYP isoforms of interest. The drug cocktail will be administered on Day -3 before the initiation of lasmiditan on Day 1, and on Day 7 concurrently with dosing of lasmiditan, when steady-state concentrations of lasmiditan should be achieved. Probe drug administration will be open-label, as the PK endpoints of the study are objective.

9.6. Pharmacodynamics

The benzodiazepine withdrawal symptom questionnaire (Tyrer et al. 1990) will be completed daily by subjects from Day 2 of lasmiditan or placebo dosing until 14 days following the final dose of lasmiditan or placebo. Whilst resident at the CRU, subjects will be administered the questionnaire by CRU staff. Subjects will be administered the questionnaire via phone by a member of CRU staff each day following discharge from the CRU on Day 9 until the follow-up visit in both cohorts. The physician withdrawal checklist (Rickels et al. 2008) will be completed by qualified CRU staff predose on Day 7 and follow-up.

10.3.3. Pharmacodynamic Evaluations

10.3.3.1. Pharmacodynamic Parameter Estimation

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

10.3.3.2. Pharmacodynamic Statistical Inference

Benzodiazepine withdrawal symptom questionnaire scores and physician withdrawal checklist will be listed, and summarized using standard descriptive statistics. Total score at each time point will be averaged for each treatment group in each cohort based upon the available data, and the lasmiditan group will be compared with the placebo group via t-test at each time point within each cohort.

11. References

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