Protocol H8H-MC-LAHD(a)

Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol

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Lasmiditan (LY573144)

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1. Protocol Synopsis

Title of Study:
Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol

Rationale:
In clinical practice, lasmiditan is likely to be coadministered with propranolol, and it is therefore pertinent to determine the potential for cardiovascular effects or pharmacokinetic (PK) drug interactions. Propranolol is known to decrease heart rate. Study H8H-MC-LAHD is being conducted to evaluate the cardiovascular effects and PK impact of coadministration of lasmiditan with propranolol in healthy subjects.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
To evaluate the effects of propranolol alone and in combination with lasmiditan on heart rate.	Heart rate by Holter ambulatory monitoring.
Secondary	
To evaluate the effects of propranolol alone and in combination with lasmiditan on blood pressure and PR interval.	PR interval by Holter ambulatory monitoring, systolic blood pressure, and diastolic blood pressure.
To explore the tolerability of a single dose of lasmiditan alone or in combination with propranolol.	A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
To evaluate the PK of lasmiditan alone and in combination with propranolol.	Maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}) and area under the concentration versus time curve (AUC) from time 0 extrapolated to infinity (AUC[0-∞]).
To evaluate the PK of propranolol alone and in combination with lasmiditan.	C_{max}, t_{max}, and area under the concentration versus time curve during 1 dosing interval (AUCτ).

Summary of Study Design:

This is an open-label, fixed-sequence study in healthy subjects to assess the cardiovascular effects of the coadministration of lasmiditan with propranolol. Subjects will receive a single dose of 200 mg lasmiditan on Day 1, then receive a single dose of 200 mg lasmiditan coadministered with steady-state propranolol on Day 9.

Blood samples will be collected predose and up to 48 hours postdose on Days 1 and 9 for the measurement of plasma concentrations of lasmiditan and its metabolites, and predose and up to 12 hours postdose on Days 8 and 9 for the measurement of plasma concentrations of propranolol.

Safety will be assessed through reporting of adverse events (AEs), clinical laboratory evaluations, vital signs measurements, 12-lead electrocardiograms (ECGs), and physical examinations.

Cardiovascular effects will be assessed by Holter ambulatory monitoring and replicate measurements of blood pressure at predose, and for 12 hours postdose on Days -1, 1, 8, and 9.

Treatment Arms and Planned Duration for an Individual Subject:
All subjects will be assigned to the same treatment sequence. The planned duration for each individual subject will be approximately 45 days, including screening.

Number of Subjects:
Approximately 44 subjects may be enrolled so that at least 36 subjects complete the study.

Statistical Analysis:

The primary parameters for the cardiovascular analyses will be systolic blood pressure, diastolic blood pressure, mean hourly heart rate, mean hourly heart rate nadirs, heart rate, and PR interval. Mean hourly heart rates from 1 hour predose to 12 hours postdose will be calculated on Days -1, 1, 8, and 9 from the Holter monitoring data. Negative chronotropic effects will be evaluated using nadir (1-6 h), nadir (>6 h–12 h), and nadir (1-12 h), which are defined as the lowest mean hourly heart rate during each postdose time period on each day. Heart rate and PR interval will also be determined on Days -1, 1, 8, and 9 from the 10-second Holter traces extracted at the time points listed in the Schedule of Activities.

Cardiovascular parameters will be evaluated to determine the impact of coadministration of propranolol with lasmiditan on blood pressure, heart rate, and PR interval compared to propranolol alone. Primary cardiovascular parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus propranolol alone [Day 8; reference treatment]), and a random effect for subject. Least squares (LS) means will be calculated for the test and reference treatments. Mean treatment differences will be presented along with the corresponding 90% confidence interval (CI). Primary PD parameters may be log-transformed prior to the statistical analysis if a review of the data indicates that the assumption of normality is violated. A similar analysis will be performed to determine the impact of coadministration of lasmiditan with propranolol on blood pressure, heart rate, and PR interval compared to lasmiditan alone. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus lasmiditan alone (Day 1; reference treatment).

The impact of coadministration of propranolol with lasmiditan on orthostatic blood pressure and pulse rate will be evaluated using descriptive statistics as appropriate. No formal statistical analysis is planned.

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and propranolol will be calculated by standard noncompartmental methods of analysis.

Pharmacokinetic parameters will be evaluated to determine the impact of propranolol coadministration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The t_{max} 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.

A similar analysis will be performed to determine the impact of coadministration of a single dose of lasmiditan on the steady-state PK of propranolol. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus propranolol alone (Day 8; reference treatment).

Safety parameters will be summarized using descriptive statistics, where appropriate.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHD

	Screening	Study Days													Follow-up/ED	Comments
Procedure	-28 to -3 days prior to Day 1	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~7 days post last dose	
Informed Consent	X															
Subject Admission to CRU		X														
Subject Discharge from CRU														X		
Lasmiditan Administration				X, indicates time = 0								X				
Propranolol Administration							X	X	X	X	X	X	X			
Medical History	X															
Height	X															
Weight	X															
Temperature	X															
Physical Exam	X		X	X		X						X		X	X	Full physical examination (to include neurological examination) at screening, Day -1 and follow-up visit only. Symptom driven physical examination for all other time points.

	Screening	Study Days													Follow-up/ED	Comments
Procedure	-28 to -3 days prior to Day 1	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~7 days post last dose	
Supine Blood Pressure and Pulse Rate (hours)	X		X	Predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12			X	X	X	X	Predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	Predose, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	X			Blood pressure and pulse rate should be assessed at predose on Days 4 to 7 and on Day 10. Time points may be added if warranted and agreed upon between Lilly and the investigator. All assessments should be performed in triplicate, with the exception of screening. See Section 9.4.2 for details. If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

	Screening	Study Days													Follow-up/ED	Comments
Procedure	-28 to -3 days prior to Day 1	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~7 days post last dose	
Orthostatic Vital Signs (hours)	X		X	Predose, 1, 2							Predose, 1, 2	Predose, 1, 2				Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes. If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture. Time points may be added if warranted and agreed upon between Lilly and the investigator.
Clinical Lab Tests (including serum pregnancy test)	X	X			X						X		X		X	See Appendix 2, Clinical Laboratory Tests, for details. If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.
12-lead ECG (hours)	X		X	Predose, 1, 2, 4	24						Predose, 1, 2, 4	Predose, 1, 2, 4	24			Single ECGs to be taken at each time point. If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

	Screening	Study Days													Follow-up/ED	Comments
Procedure	-28 to -3 days prior to Day 1	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~7 days post last dose	
Holter Ambulatory Monitoring			X	X							X	X				Ambulatory monitoring through the 12-hour time point on Days -1, 1, 8, and 9. Monitoring on Day -1 should be started approximately 1 hour prior to the anticipated dosing time. Extractions should be made at -1, 0.5, 1, 2, 2.5, 3, 4, 6, 8, and 12 hours postdose. Triplicate ECG extractions to be taken at each time point.
Genetic Sample		X														Single sample for pharmacogenetic analysis taken prior to/on Day 1
Lasmiditan and Metabolite PK Samples (hours)				Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48						Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48		Sampling times are relative to the time of study treatment administration (0 min). If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

	Screening	**Study Days**													**Follow-up/ED**	**Comments**
Procedure	-28 to -3 days prior to Day 1	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~7 days post last dose	
Propranolol PK Samples (hours)											Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12				Sampling times are relative to the time of propranolol administration (0 min). If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; min = minutes; PK = pharmacokinetics.

3. Introduction

3.1. Study Rationale

Lasmiditan is a small molecule serotonin (5-hydroxytryptamine; 5-HT)$_{1F}$ receptor agonist being developed for the acute treatment of migraine. When administered intravenously (IV) at the highest dose of 180 mg (H8H-BD-LACA), lasmiditan produced a small but statistically significant dose-related decrease in heart rate and increase in blood pressure, although the magnitude of these effects was considered unlikely to be of clinical significance. Following oral administration at doses of up to 400 mg, heart rate again was slightly reduced, but there were no consistent effects on blood pressure. The effects on vital signs were transient, not dose related, and unlikely to be clinically significant given the intended intermittent use of lasmiditan.

Propranolol is a non-selective β-adrenergic receptor antagonist that is given for migraine prophylaxis. In clinical practice, lasmiditan is likely to be coadministered with propranolol; it is therefore pertinent to determine the potential for cardiovascular effects or pharmacokinetic (PK) drug interactions. β-adrenergic receptor antagonists (such as propranolol) are known to decrease heart rate by approximately 17 to 18% (LeWinter et al 1975).

Propranolol metabolism involves multiple cytochrome P450 (CYP) pathways, specifically via CYP2D6, CYP1A2, and CYP2C19, while it is a weak inhibitor of CYP2D6. Propranolol may also be a moderate inhibitor of CYP1A2 based on its interaction with theophylline, a sensitive CYP1A2 substrate (Miners et al. 1985). Although the major route of lasmiditan metabolism in humans is non-CYP mediated ketone reduction, minor CYP-mediated metabolism via CYP1A2 and CYP3A4 was noted in vitro. In vitro, lasmiditan has been shown to be a weak CYP2D6 inhibitor which is not expected to be clinically significant. Taken together, there is a low likelihood of a pharmacokinetic interaction between lasmiditan and propranolol.

Study LAHD is being conducted to evaluate the cardiovascular effects and PK impact of coadministration of a single dose of lasmiditan 200 mg with propranolol 80 mg twice daily (bid) in healthy subjects.

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 IV formulation, 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 patients were randomized to 100 mg lasmiditan (630 subjects), 200 mg (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 pain free rate and the relief of most 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 213 healthy subjects in five Phase 1 studies: as IV doses ranging from 0.1 to 180 mg (H8H-MC-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 400 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 study (COL MIG-301), 1856 patients aged 18 to 79 years received at least 1 dose of lasmiditan or placebo, with 1239 patients receiving oral tablets of 100 or 200 mg lasmiditan. The most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) included dizziness (12.5 to 16.3%), paresthesia (5.7 to 7.9%), somnolence (5.4 to 5.7%), fatigue (3.1 to 4.1%), , and, compared to placebo where 3.4%, 2.1%, 2.3%, and 0.3% of subjects reported each event, respectively. The majority of these TEAEs were mild or moderate in severity and none led to subject withdrawal.

Oral tablet doses of lasmiditan up to 400 mg did not result in any clinically relevant changes in ECGs (including QT interval/corrected QT interval [QTc]) or vital signs following administration to healthy subjects. There was a consistent small decrease in heart rate at oral doses of 100 to 400 mg lasmiditan though this was not considered to be clinically significant (COL MIG-102, COL MIG-103, COL MIG-105). A single SAE of dizziness with sinus bradycardia after an oral dose of 200 mg lasmiditan was reported; this event was moderate in severity, occurred approximately 30 minutes after dosing with lasmiditan 200 mg, and was considered to be probably related to lasmiditan. The subject was admitted to hospital for overnight observation following review by the hospital emergency room physician.

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 doses ranging from 25 to 400 mg, and the geometric mean terminal half-life was approximately 4 to 6 hours. Lasmiditan exhibited dose-linear PK; low to moderate inter-subject variability in exposure was observed across doses (coefficient of variation [%CV] up to 61% and 45% for maximum observed drug concentration [C_{max}] and area under the curve [AUC], respectively (COL MIG-102). Renal clearance of lasmiditan was low, with approximately 2% of the parent dose recovered by 24 hours postdose. Co-administration of lasmiditan with a high fat diet led to a delay in median time of maximum observed drug concentration (t_{max}) value by approximately 1 hour and a modest (~20%) increase in lasmiditan maximum observed drug concentration (C_{max}) and AUC values, relative to that under fasted conditions.

Human metabolism has been investigated using liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) following oral dosing with lasmiditan, where up to 11 metabolites were detected in plasma and urine, including 3 major metabolites (M7, M8, and M18). These metabolites lacked significant pharmacological activity at the 5-HT_{1F} receptor and were generally considered to be pharmacologically inactive. The relative proportions of metabolites to intact lasmiditan remained reasonably constant throughout the oral dose range

studied and their PK was approximately linear. The half-life of the metabolites ranged from ~4.5 hours to >12 hours.

3.3. Benefit/Risk Assessment

In this study, the effects of propranolol alone, lasmiditan alone, and propranolol in combination with lasmiditan on blood pressure, heart rate, and PR interval will be evaluated in healthy subjects. There is no anticipated therapeutic benefit for the subjects.

Lasmiditan has been tolerated by healthy subjects as single oral doses up to 400 mg. No clinically significant safety or tolerability concerns have been identified in subjects to date for lasmiditan up to the highest single oral dose given (400 mg). Dosing of lasmiditan in this study will be conducted in an inpatient setting, and subjects will be monitored in house for at least 48 hours after dosing.

Propranolol is a marketed drug and will be administered within the recommended dose regimen for clinical use (80 mg bid); this dose regimen has been tolerated in previous PK/PD studies in healthy subjects (for example, Fleishaker et al. 2001; Marathe et al. 1998; Peck et al. 1997; Scott et al. 1991). Dosing of propranolol in this study will be conducted in an inpatient setting, and subjects will be monitored in house for at least 24 hours after completing dosing.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated adverse events (AEs) of lasmiditan are to be found in the Investigator's Brochure (IB).

More detailed information about the known and expected benefits and risks of propranolol may be found in the following: Patient Information Leaflet or Summary of Product Characteristics.

4. Objectives and Endpoints

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

Table LAHD.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the effects of propranolol alone and in combination with lasmiditan on heart rate.	Heart rate by Holter ambulatory monitoring.
Secondary	
To evaluate the effects of propranolol alone and in combination with lasmiditan on blood pressure and PR interval.	PR interval by Holter ambulatory monitoring, systolic blood pressure, and diastolic blood pressure.
To explore the tolerability of a single dose of lasmiditan alone or in combination with propranolol.	A summary of the number of TEAEs and SAEs.
To evaluate the PK of lasmiditan alone and in combination with propranolol.	C_{max}, t_{max}, and AUC(0-∞).
To evaluate the PK of propranolol alone and in combination with lasmiditan.	C_{max}, t_{max}, and AUC during 1 dosing interval (AUCτ).
Exploratory Objectives	
To evaluate the effects of lasmiditan alone and in combination with propranolol on orthostatic changes in blood pressure and pulse rate.	Orthostatic changes in systolic blood pressure, diastolic blood pressure, and pulse rate.
To evaluate the PK of the metabolites M8, M7, and M18 in healthy subjects following a single 200-mg oral dose of lasmiditan alone and in combination with propranolol.	PK parameters: C_{max}, t_{max}, and AUC(0-∞)

5. Study Design

5.1. Overall Design

This is an open-label, fixed-sequence study in healthy subjects to assess the cardiovascular effects of coadministration of lasmiditan with propranolol.

Screening Period:

All subjects will participate in a screening visit up to 28 days prior to the first lasmiditan dose.

Dosing Period:

Subjects will be admitted to the clinical research unit (CRU) on Day -2. On Day 1, subjects will receive a single dose of 200 mg lasmiditan, then receive propranolol (immediate release formulation; half-life approximately 3 to 6 hours) 80 mg bid on Days 4 through 10 and a single dose of 200 mg lasmiditan coadministered with propranolol on Day 9. Subjects will reside in the CRU from Day -2 until Day 11 when they may be discharged from the CRU following completion of all study procedures, at the investigator's discretion.

Study governance considerations are described in detail in Appendix 3.

Blood samples will be collected predose and up to 48 hours postdose on Days 1 and 9 for the measurement of plasma concentrations of lasmiditan and its metabolites. Blood samples will also be collected predose and up to 12 hours postdose on Days 8 and 9 for the measurement of plasma concentrations of propranolol.

Safety assessments performed during the study will include AEs, clinical laboratory evaluations, vital signs measurements, 12-lead ECGs, and physical examinations.

Cardiovascular effects will be assessed by Holter ambulatory monitoring and replicate measurements of blood pressure at predose, and for 12 hours postdose on Days -1, 1, 8, and 9.

Follow-up Period

Subjects will attend a follow-up visit approximately 7 days after the last dose.

Figure LAHD.1 illustrates the study design.

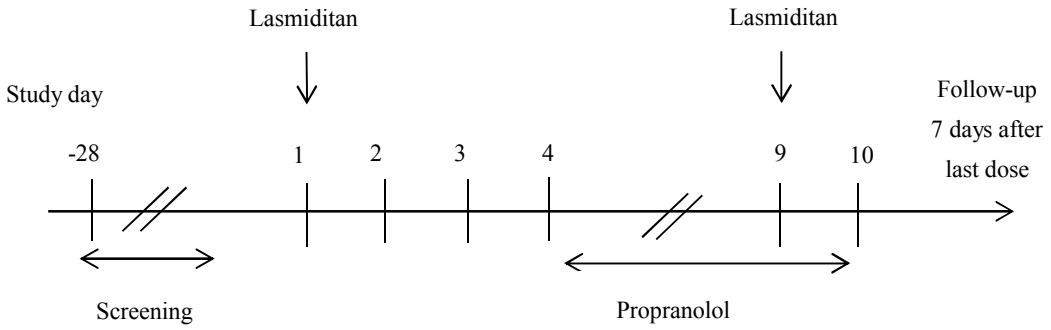

Figure LAHD.1. Illustration of study design for Protocol H8H-MC-LAHD.

5.2. Number of Participants

Approximately 44 subjects may be enrolled so that at least 36 subjects complete the study.

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

The study has an open-label, fixed-sequence design in which each subject receives lasmiditan alone, propranolol alone, and lasmiditan coadministered with propranolol, allowing each subject to act as his/her own control for safety and PK comparisons. A single 200 mg dose of lasmiditan was selected as it is the highest potential recommended dose for lasmiditan. The washout period between lasmiditan doses of 8 days is considered sufficient based on the half-life of lasmiditan of approximately 4 to 6 hours. Propranolol takes approximately 1 to 4 hours to reach maximum concentrations in the blood and has a plasma half-life of approximately 3 to 6 hours, although its biological effects may last longer (Propranolol SPC, 2016); therefore, it will be administered according to a twice daily (bid) dosing regimen. Propranolol will be administered twice daily for 7 days, with a single dose of lasmiditan coadministered on the 6th day, to ensure that propranolol concentrations are at steady-state at the time of lasmiditan dosing and throughout the lasmiditan PK sampling period (48 hours postdose).

5.5. Justification for Dose

The dose level of 200 mg lasmiditan has been well tolerated in previous studies of healthy subjects. This dose level is expected to be the highest potential recommended single dose for lasmiditan.

The dose of propranolol (80 mg bid) is within the range used in clinical practice, and this dose regimen has been tolerated by healthy subjects in previous PK/PD studies (for example, Fleishaker et al. 2001; Marathe et al. 1998; Peck et al. 1997; Scott et al. 1991).

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 to 28 days prior to enrollment (Day 1). 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/or enrollment:

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

[1a] male subjects:

are not required to adhere to contraceptive 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 last dose of lasmiditan. Reliable methods of contraception for female subjects of childbearing potential include the use of stable hormonal contraception, bilateral tubal ligation, intrauterine device, or diaphragm with spermicide along with male partner's use of male condom with spermicide.

of non-childbearing 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 (HRT).

[2] are aged 18 to 65 years old at the time of screening.

[3] have a body mass index (BMI) of 19.0 to 35.0 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 with acceptable deviations that are judged to be not clinically significant by the investigator.

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

[6] are 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.

[9] are Lilly or Covance employees.

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

[11] have known allergies to lasmiditan, propranolol, related compounds or any components of the formulation of lasmiditan or propranolol.

[12] are persons who have previously received the investigational product in this study, withdrawn from this study or received lasmiditan in any other study investigating lasmiditan.

[13] have participated (dosed with investigational product), within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[14] have as history of, or ECG findings of, clinically significant bradycardia, heart block, tachy or brady arrhythmias, sick sinus syndrome/sinoatrial block, or second or third-degree heart block, or have any other abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study.

[15] have an abnormal supine blood pressure, defined as systolic blood pressure <95 or >140 mmHg or diastolic blood pressure <65 or >90 mmHg at screening. After screening, vital sign eligibility will be done at the discretion of the investigator. Additional assessments may be performed to confirm eligibility.

[16] have a history of syncope, presyncope, uncontrolled vertigo, postural dizziness, or at risk for falls, as judged to be clinically significant by the investigator, or have orthostatic decreases in systolic blood pressure of >20 mmHg, or have orthostatic decreases in diastolic blood pressure of >10 mmHg at screening. May be repeated if asymptomatic.

[17] have a supine pulse rate of <50 or >90 bpm at screening. Up to 2 additional assessments may be performed to confirm eligibility.

[18] have an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2.

[19] have significant history of or current cardiovascular, respiratory (including bronchospasm or bronchial asthma, or chronic obstructive airways disease), 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 medication; or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable.

[20] have a history of or current pheochromocytoma.

[21] show evidence of significant active neuropsychiatric disease (for example, manic depressive illness, schizophrenia, depression).

[22] show a history of central nervous system (CNS) conditions such as strokes, transient ischaemic 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.

[23] currently use, or within the past 1 year used recreational drugs, or showed evidence of substance dependence within the past 6 months based on history at screening visit.

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

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

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

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

[28] intend to use over-the-counter or prescription medication, dietary supplements within 14 days prior to dosing and until study discharge (apart from occasional acetaminophen or HRT).

[29] have donated blood of more than 500 mL within 1 month prior to the screening visit.

[30] have an average weekly alcohol intake that exceeds 21 units per week (males aged up to 65 years) and 14 units per week (females and males over 65 years), or are unwilling to stop alcohol consumption 48 hours prior to dosing and whilst resident at the CRU. At all other times, subjects must consume no more than 2 units per day (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).

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

[32] are unwilling to refrain from tobacco- or nicotine-containing products from 3 months prior to screening until discharge from the study.

[33] Have any history or hypersensitivity to food or medications.

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [1] through [7] define a healthy population suitable for evaluation in a Phase 1 study. Criteria [8] and [9] prevent conflict of interest in study participants. Criteria [10] through [33] predominantly exclude medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints.

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 and propranolol will be administered after an overnight fast of at least 8 hours. On intensive PK sampling days (Days 1, 8 and 9), 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, at which time a meal will be served.

Subjects may be permitted to consume a light breakfast at 1 hour postdose at the discretion of the investigator on all other days.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine – Subjects will refrain from consuming xanthine- or caffeine-containing food and drinks from 48 hours prior to admission, and while resident at the CRU.

Alcohol – Subjects will not consume alcohol for 48 hours prior to admission, and while resident at the CRU. At all other times, subjects must consume no more than 2 units per day (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).

Tobacco – Subjects will refrain from smoking from 3 months prior to screening until discharge from the study.

Grapefruit – Subjects will refrain from consuming grapefruit and grapefruit-containing products from 7 days prior to Day 1 and until study discharge.

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 re-screened.

7. Treatment

7.1. Treatment Administered

Investigational products used in this study are shown in Table LAHD.2.

Tablets of lasmiditan and propranolol will be administered orally with approximately 240 mL of room temperature water, in a sitting position. Tablets of lasmiditan will be administered in the morning of each dosing day, and tablets of propranolol will be administered in the morning and evening, approximately 12 hours apart, of each dosing day. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table LAHD.2. Treatments Administered

Treatment Name	Lasmiditan	Propranolol
Dosage Formulation	film-coated tablet	film-coated tablet
Unit Dose Strength/Dosage Level	(1 × 200-mg) tablets/ 200 mg lasmiditan	(1 × 80-mg) tablets/ 80 mg propranolol
Route of Administration	Oral	Oral
Dosing Instructions	1 tablet taken in the morning of Days 1 and 9	1 tablet taken in the morning and evening of Days 4-10

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel;
- verifying that instructions are followed properly;
- maintaining accurate records of investigational product dispensing and collection;
- 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 supplies in bottles. Propranolol will be sourced by the investigative site.

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

7.2. Method of Treatment Assignment

All subjects will receive the same treatments in the same sequence.

7.2.1. Timing of Doses

Doses of propranolol will be administered at approximately the same time on each dosing day (every 12 hours). On study days where lasmiditan and propranolol are coadministered (Day 9), propranolol should be administered immediately prior to the lasmiditan dose. Both lasmiditan doses should be administered at approximately the same time of day. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose modification will not be allowed during the study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm all investigational product 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 investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

In general, concomitant medication should be avoided; however, acetaminophen (maximum 2 g/24 hours) may be administered at the discretion of the investigator for treatment of headaches etc. Contraceptive medication is permitted as per the inclusion criteria. Hormone replacement therapy is also allowed.

If the need for concomitant medication (other than acetaminophen or HRT) 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

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason must complete adverse event and follow-up procedures per Section 9.2 of this protocol.

8.1. Discontinuation from Study Treatment

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:

- alanine aminotransferase (ALT), aspartate aminotransferase (AST) >5× ULN (upper limit of normal)
- ALT or AST >3× ULN sustained for more than 2 weeks
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or INR >1.5
- ALT or AST >3× ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3× ULN
- ALP>2.5× ULN and TBL >2× 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, a discussion must occur between the Lilly clinical pharmacologist/CRP or designee and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist/CRP or designee to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
- Subject Decision
    - the subject requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for a scheduled visit 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 informed consent form (ICF) is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions. 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 concomitant treatment or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product and/or 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.

9.2.1. Serious Adverse Events

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

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

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

Additionally, study site personnel must alert Lilly Global Subject 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 eCRF 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 investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product 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.

9.4. Safety

9.4.1. Laboratory Tests

For each subject, clinical 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). Vital signs measurements should be conducted within approximately 20 minutes of the nominal timepoint.

Blood pressure and pulse rate should be measured after at least 5 minutes supine. All supine blood pressure and pulse rate measurements except for screening will be done in triplicates at approximately 1-minute intervals. Where possible, the last triplicate vital sign can be used as the supine vital sign for the calculation of orthostatic changes. Vital signs measurements should be taken from the non-dominant and opposite arm as used for PK sampling whenever possible, and for each individual subject the same cuff size should be used throughout the study for measurements of blood pressure.

Where orthostatic measurements are required, subjects should be supine for at least 5 minutes, and then subjects should stand, and standing blood pressure will be measured after 2 minutes; no longer than 3 minutes.

In the event of a positive asymptomatic orthostatic response, repeats are at the investigator's discretion.

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 if warranted.

9.4.3. Electrocardiograms

9.4.3.1. 12-Lead Electrocardiograms

For each subject, single 12-lead digital safety ECGs will be collected according to the Schedule of Activities (Section 2). Electrocardiograms should be collected within approximately

20 minutes of the nominal timepoint. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. 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 quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether 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 evaluation from at least 1 of the replicate ECGs from each time point.

It is recognized that the ECG interpretations by the investigator (or qualified designee) and the cardiologist at the central ECG laboratory may be different. Interpretation of the ECG by the investigator (or qualified designee) will be used for study entry and immediate subject management.

9.4.3.2. Holter Ambulatory Monitoring

Continuous 12-lead Holter recordings over 12 hours will be performed according to the Schedule of Activities (Section 2). Extractions should be performed within approximately 30 minutes of the nominal timepoint.

Subjects must be in a quiet atmosphere without significant external stimulation (TV, internet, etc.), in a supine position for at least 5 to 10 minutes before the specified ECG collection times indicated in the Schedule of Activities, and remain supine but awake during ECG collection and for at least 10 minutes afterward. Subjects should be encouraged to remain still, if possible, during this time.

Digital recordings of all periods of continuous ECG recordings in individual subjects will be transferred to a central ECG laboratory designated by Lilly. The ECG laboratory will perform quality control checks for the time points of interest (for example, acquisition quality for ability to measure/interpret, demographics, and study details) and extract 3 unique 10-second ECGs at the times listed in the Schedule of Activities (Section 2).

The ECG laboratory will then store the 12-hour recording as well as the extracted 10-second ECGs, and a cardiologist at the central ECG laboratory will conduct a full overread (including the measurement of all intervals) on one of the replicates that were extracted. For each set of replicates, the cardiologist will determine the RR and QT intervals and heart rate on the ECGs

that were not fully overread. No reports will be issued from the central ECG laboratory back to the sites for any ECGs.

All data from the overreads will be placed in a Lilly or Contract Research Organization database for analytical and study report purposes.

Interpretations of the ECG at the central laboratory will be used for data analysis and report-writing purposes.

9.4.4. 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

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

9.4.4.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated total bilirubin ≥2× ULN, hepatic monitoring tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, conjugated bilirubin, gamma-glutamyl transferase (GGT), and creatinine phosphokinase (CPK) 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 ≥ 5× ULN on two or more consecutive blood tests
- elevated serum TBL to ≥ 2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ 2× ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan and its metabolites, and venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of propranolol. A maximum of 3 samples each may be collected for analysis of lasmiditan or propranolol at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.5.1. Bioanalysis

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

Concentrations of lasmiditan and 3 major metabolites will be assayed using a validated LC-MS/MS method.

Concentrations of propranolol will be assayed using a validated LC-MS/MS method.

Bioanalytical samples collected to measure investigational product and metabolite 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 such as metabolism and/or protein binding work.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

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

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable exposure or response to lasmiditan and to investigate genetic variants thought to play a role in migraine. 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.

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 44 subjects may be enrolled to ensure 36 subjects complete the study. Assuming a standard deviation for the change in heart rate of 10.9 (based on previous studies [H8H-MC-CD-LAHO and H8H-CD-LAHJ]), this will result in a 90% probability that the half-width of the 90% CI about the mean within-subject change is no larger than 5 bpm.

Subjects who are randomized but do not complete the study may be replaced to ensure that enough subjects complete the study.

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 data from all subjects who receive at least one dose of lasmiditan or propranolol and have evaluable PK.

Cardiovascular analyses will be conducted on data from all subjects who have the relevant test and reference treatment measurements.

Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

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 investigational product 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 investigational product 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 investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Clinical laboratory parameters, vital signs, and 12-lead ECG parameters will be listed, and summarized using standard descriptive statistics. 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, its metabolites, and propranolol will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be: C_{max}, t_{max}, and AUC(0-∞) of lasmiditan and its metabolites on Days 1 and 9; and C_{max}, t_{max}, and AUC_{τ} of propranolol on Days 8 and 9. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to determine the impact of propranolol coadministration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The t_{max} 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.

A similar analysis will be performed to determine the impact of coadministration of a single dose of lasmiditan on the steady-state PK of propranolol. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus propranolol alone (Day 8; reference treatment).

Additional analyses may be performed, as warranted.

10.3.3. Cardiovascular Analyses

10.3.3.1. Cardiovascular Parameter Estimation

The primary parameters for the cardiovascular analyses will be systolic blood pressure, diastolic blood pressure, mean hourly heart rate, mean hourly heart rate nadirs, heart rate, and PR interval. Mean hourly heart rates from 1 hour predose to 12 hours postdose will be calculated on Days -1, 1, 8, and 9 from the Holter monitoring data. Negative chronotropic effects will be evaluated

using nadir (1–6 h), nadir (>6 h–12 h), and nadir (1–12 h), which are defined as the lowest mean hourly heart rate during each postdose time period on each day. Heart rate and PR interval will also be determined on Days -1, 1, 8, and 9 from the 10-second Holter traces extracted at the time points listed in the Schedule of Activities (Section 2).

Orthostatic changes in blood pressure and pulse rate will be determined at the time points listed in the Schedule of Activities (Section 2)

10.3.3.2. Statistical Inference of Cardiovascular Parameters

Cardiovascular parameters will be evaluated to determine the impact of coadministration of propranolol with lasmiditan on blood pressure, heart rate, and PR interval compared to propranolol alone. Primary cardiovascular parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus propranolol alone [Day 8; reference treatment]), and a random effect for subject. Least squares means will be calculated for the test and reference treatments. Mean treatment differences will be presented, along with the corresponding 90% CI. Primary PD parameters may be log-transformed prior to the statistical analysis if a review of the data indicates that the assumption of normality is violated.

A similar analysis will be performed to determine the impact of coadministration of lasmiditan with propranolol on blood pressure, heart rate, and PR interval compared to lasmiditan alone. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus lasmiditan alone (Day 1; reference treatment).

The impact of coadministration of propranolol with lasmiditan on orthostatic blood pressure and pulse rate will be evaluated using descriptive statistics as appropriate. No formal statistical analysis is planned.

10.3.4. Interim Analyses

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

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine (serotonin)
AE	adverse event: Any untoward medical occurrence in a subject 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 aminotranferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
AUC_T	area under the concentration versus time curve during 1 dosing interval
bid	twice daily
BMI	body mass index
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed drug concentration
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety 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 time point, depending on the steps required to obtain confirmed results.
CPK	creatine phosphokinase
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
CV%	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
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.
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 with tandem mass spectrometric detection

LS	least squares
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PK	pharmacokinetic
QTc	corrected QT interval
randomize	the process of assigning subjects to an experimental group on a random basis
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 of maximum observed drug concentration

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)	Glucose (random)
Platelets	Blood urea nitrogen (BUN)
Differential WBC absolute counts and % of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
	Creatinine
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	Ethanol testing[b]
Ketones	Urine drug screen[b]
Bilirubin	Hepatitis B surface antigen[a]
Urobilinogen	Hepatitis C antibody[a]
Blood	HIV[a]
Nitrite	Serum pregnancy test (females only)[d]
Urine microscopic (if positive result for blood)	FSH (females only, if applicable)[c]

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

[a] Performed at screening only.

[b] Urine drug screen and ethanol level will be performed locally at screening and may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities (Section 2).

[c] Performed at screening only, for confirmation of postmenopausal status.

[d] Performed at screening only, Day -1, and follow-up only.

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 International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

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

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

3) applicable laws and regulations

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

Protocol Signatures

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

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 eCRFs, 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 eCRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

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

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with subjects in consultation with Lilly or its designee 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**
CPK	**antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood 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, clinical laboratory tests, and bioanalytical assays) during the study.

Protocol H8H-MC-LAHD Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	19.5	1	19.5
Clinical laboratory tests[a]	12.5	6	75
Lasmiditan and metabolite PK[b]	2	31	62
Propranolol PK[b]	4	23	92
Pharmacogenetics	10	1	10
Total			258.5
Total for clinical purposes (rounded up to the nearest 10 mL)			260

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

[b] Includes a potential 3 additional samples.

Appendix 6. Protocol Amendment H8H-MC-LAHD(a) Summary: Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol

Overview

Protocol H8H-MC-LAHD, Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are as follows:

- Following feedback from the FDA from the Type C meeting on 12 October 2017, the protocol was amended to include an assessment of lasmiditan metabolites.
- Subjects should be admitted to the CRU on Day -2. The language in Section 5.1 has been updated to remove contradictory information that preceded "Day -2".
- Clinical laboratory assessments and genetic sampling in the Schedule of Activities should be performed on Day -2 to allow determination of a dosing order prior to Holter monitoring on Day -1.
- Pregnancy tests are required only at screening, Day -1, and the follow up visit; the safety laboratory test appendix was updated accordingly.
- Subjects should be excluded from the study if they have orthostatic decreases in systolic blood pressure of >20 mmHg, not supine blood pressure as is stated in the original protocol.
- The alcohol restriction in this study should be observed from 48 hours prior to CRU admission and until discharge from the CRU, as described in Section 6.3.2. The exclusion criterion was updated to be consistent with this language.

Revised Protocol Sections

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

1. Protocol Synopsis

Summary of Study Design:

This is an open-label, fixed-sequence study in healthy subjects to assess the cardiovascular effects of the coadministration of lasmiditan with propranolol. Subjects will receive a single dose of 200 mg lasmiditan on Day 1, then receive a single dose of 200 mg lasmiditan coadministered with steady-state propranolol on Day 9.

Blood samples will be collected predose and up to 48 hours postdose on Days 1 and 9 for the measurement of plasma concentrations of lasmiditan and its metabolites, and predose and up to 12 hours postdose on Days 8 and 9 for the measurement of plasma concentrations of propranolol.

Statistical Analysis:

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and propranolol will be calculated by standard noncompartmental methods of analysis.

Pharmacokinetic parameters will be evaluated to determine the impact of propranolol coadministration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHD

	Screening	**Study Days**													**Follow-up/ED**	**Comments**
Procedure	-28 to -3 days prior to Day 1	-2	-1	1	2	3	4	5	6	7	8	9	10	11	~7 days post last dose	
Clinical Lab Tests (including serum pregnancy test)	X	X	~~X~~		X						X		X		X	See Appendix 2, Clinical Laboratory Tests, for details. If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.
Genetic Sample		X	~~X~~													Single sample for pharmacogenetic analysis taken prior to/on Day 1
Lasmiditan and Metabolite PK Samples (hours)				Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48						Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48		Sampling times are relative to the time of study treatment administration (0 min). If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

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 IV formulation, 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 patients were randomized to 100 mg lasmiditan (630 subjects), 200 mg (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 pain free rate and the relief of most 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 213 healthy subjects in five Phase 1 studies: as IV doses ranging from 0.1 to 180 mg (H8H-MC-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 400 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 study (COL MIG-301), 1856 patients aged 18 to 79 years received at least 1 dose of lasmiditan or placebo, with 1239 patients receiving oral tablets of 100 or 200 mg lasmiditan. The most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) included dizziness (12.5 to 16.3%), paresthesia (5.7 to 7.9%), somnolence (5.4 to 5.7%), fatigue (3.1 to 4.1%), , and, compared to placebo where 3.4%, 2.1%, 2.3%, and 0.3% of subjects reported each event, respectively. The majority of these TEAEs were mild or moderate in severity and none led to subject withdrawal.

Oral tablet doses of lasmiditan up to 400 mg did not result in any clinically relevant changes in ECGs (including QT interval/corrected QT interval [QTc]) or vital signs following administration to healthy subjects. There was a consistent small decrease in heart rate at oral doses of 100 to 400 mg lasmiditan though this was not considered to be clinically significant (COL MIG-102, COL MIG-103, COL MIG-105). A single SAE of dizziness with sinus bradycardia after an oral dose of 200 mg lasmiditan was reported; this event was moderate in severity, occurred approximately 30 minutes after dosing with lasmiditan 200 mg, and was considered to be probably related to lasmiditan. The subject was admitted to hospital for overnight observation following review by the hospital emergency room physician.

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 doses ranging from 25 to 400 mg, and the geometric mean terminal half-life was approximately 4 to 6 hours. Lasmiditan exhibited dose-linear PK; low to moderate

inter-subject variability in exposure was observed across doses (coefficient of variation [%CV] up to 61% and 45% for maximum observed drug concentration [C_{max}] and area under the curve [AUC], respectively (COL MIG-102). Renal clearance of lasmiditan was low, with approximately 2% of the parent dose recovered by 24 hours postdose. Co-administration of lasmiditan with a high fat diet led to a delay in median time of maximum observed drug concentration (t_{max}) value by approximately 1 hour and a modest (~20%) increase in lasmiditan maximum observed drug concentration (C_{max}) and AUC values, relative to that under fasted conditions.

Human metabolism has been investigated using liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) following oral dosing with lasmiditan, where up to 11 metabolites were detected in plasma and urine, including 3 major metabolites (M7, M8, and M18). These metabolites lacked significant pharmacological activity at the 5-HT_{1F} receptor and were generally considered to be pharmacologically inactive. The relative proportions of metabolites to intact lasmiditan remained reasonably constant throughout the oral dose range studied and their PK was approximately linear. The half-life of the metabolites ranged from ~4.5 hours to >12 hours.

4. Objectives and Endpoints

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

Table LAHD.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the effects of propranolol alone and in combination with lasmiditan on heart rate.	Heart rate by Holter ambulatory monitoring.
Secondary To evaluate the effects of propranolol alone and in combination with lasmiditan on blood pressure and PR interval.	PR interval by Holter ambulatory monitoring, systolic blood pressure, and diastolic blood pressure.
To explore the tolerability of a single dose of lasmiditan alone or in combination with propranolol.	A summary of the number of TEAEs and SAEs.
To evaluate the PK of lasmiditan alone and in combination with propranolol.	C_{max}, t_{max}, and AUC(0-∞).
To evaluate the PK of propranolol alone and in combination with lasmiditan.	C_{max}, t_{max}, and AUC during 1 dosing interval (AUCτ).
Exploratory Objectives To evaluate the effects of lasmiditan alone and in	Orthostatic changes in systolic blood pressure, diastolic

combination with propranolol on orthostatic changes in blood pressure and pulse rate.	blood pressure, and pulse rate.
To evaluate the PK of the metabolites M8, M7, and M18 in healthy subjects following a single 200-mg oral dose of lasmiditan alone and in combination with propranolol.	PK parameters: C_{max}, t_{max}, and AUC(0-∞)

5.1. Overall Design

This is an open-label, fixed-sequence study in healthy subjects to assess the cardiovascular effects of coadministration of lasmiditan with propranolol.

Screening Period:

All subjects will participate in a screening visit up to 28 days prior to the first lasmiditan dose.

Dosing Period:

Subjects will be admitted to the clinical research unit (CRU) on ~~the day prior to dosing (~~Day -2~~)~~. On Day 1, subjects will receive a single dose of 200 mg lasmiditan, then receive propranolol (immediate release formulation; half-life approximately 3 to 6 hours) 80 mg bid on Days 4 through 10 and a single dose of 200 mg lasmiditan coadministered with propranolol on Day 9. Subjects will reside in the CRU from Day -2 until Day 11 when they may be discharged from the CRU following completion of all study procedures, at the investigator's discretion.

Study governance considerations are described in detail in Appendix 3.

Blood samples will be collected predose and up to 48 hours postdose on Days 1 and 9 for the measurement of plasma concentrations of lasmiditan and its metabolites. Blood samples will also be collected predose and up to 12 hours postdose on Days 8 and 9 for the measurement of plasma concentrations of propranolol.

6.2. Exclusion Criteria

[16] have a history of syncope, presyncope, uncontrolled vertigo, postural dizziness, or at risk for falls, as judged to be clinically significant by the investigator, or have orthostatic decreases in ~~supine~~ systolic blood pressure of >20 mmHg, or have orthostatic decreases in diastolic blood pressure of >10 mmHg at screening. May be repeated if asymptomatic.

[30] have an average weekly alcohol intake that exceeds 21 units per week (males aged up to 65 years) and 14 units per week (females and males over 65 years), or are unwilling to stop alcohol consumption 48 hours prior to dosing ~~until the completion of the study~~ and whilst resident at the CRU. At all other times, subjects must consume no more than 2 units per day (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).

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan and its metabolites, and venous blood samples of approximately 2 mL each will be

collected to determine the plasma concentrations of propranolol. A maximum of 3 samples each may be collected for analysis of lasmiditan or propranolol at additional time points during the study if warranted and agreed upon between both the investigator and sponsor.

Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

9.5.1. Bioanalysis

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

Concentrations of lasmiditan and 3 major metabolites will be assayed using a validated ~~liquid chromatography with tandem mass spectrometric detection (~~LC-MS/MS~~)~~ method.

Concentrations of propranolol will be assayed using a validated LC-MS/MS method.

Bioanalytical samples collected to measure investigational product and metabolite 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 such as metabolism and/or protein binding work.

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and propranolol will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be: C_{max}, t_{max}, and AUC(0-∞) of lasmiditan and its metabolites on Days 1 and 9; and C_{max}, t_{max}, and AUC_{τ} of propranolol on Days 8 and 9. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to determine the impact of propranolol coadministration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with a fixed effect for treatment (lasmiditan coadministered with propranolol [Day 9; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% CI.

The t_{max} 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.

A similar analysis will be performed to determine the impact of coadministration of a single dose of lasmiditan on the steady-state PK of propranolol. The model will include the following treatments: propranolol coadministered with lasmiditan (Day 9; test treatment) versus propranolol alone (Day 8; reference treatment).

Additional analyses may be performed, as warranted.

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)	Glucose (random)
Platelets	Blood urea nitrogen (BUN)
Differential WBC absolute counts and % of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
	Creatinine
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	Ethanol testing[b]
Ketones	Urine drug screen[b]
Bilirubin	Hepatitis B surface antigen[a]
Urobilinogen	Hepatitis C antibody[a]
Blood	HIV[a]
Nitrite	Serum pregnancy test (females only)[d]
Urine microscopic (if positive result for blood)	FSH (females only, if applicable)[c]

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

[a] Performed at screening only.

[b] Urine drug screen and ethanol level will be performed locally at screening and may be repeated prior to admission to the clinical research unit and at other times indicated in the Schedule of Activities (Section 2).

[c] Performed at screening only, for confirmation of postmenopausal status.

[d] Performed at screening only, Day -1, and follow-up only.

Appendix 5. Blood Sampling Summary

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

Protocol H8H-MC-LAHD Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	19.5	1	19.5
Clinical laboratory tests[a]	12.5	6	75
Lasmiditan and metabolite PK[b]	2	31	62
Propranolol PK[b]	4	23	92
Pharmacogenetics	10	1	10
Total			258.5
Total for clinical purposes (rounded up to the nearest 10 mL)			260

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

[b] Includes a potential 3 additional samples.