Protocol H8H-MC-LAIG

A Study to Investigate the Cardiovascular Effects of Lasmiditan in Healthy Elderly Subjects

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A Study to Investigate the Cardiovascular Effects of Lasmiditan in Healthy Elderly Subjects

Lasmiditan (LY573144)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Protocol Synopsis

Title of Study:
A Study to Investigate the Cardiovascular Effects of Lasmiditan in Healthy Elderly Subjects

Rationale:
Study H8H-MC-LAHA (LAHA) was recently conducted to determine the pharmacokinetics (PK) and safety of lasmiditan in elderly and young healthy subjects following a single oral administration of lasmiditan 200 mg. The study database has been locked but the clinical study report has not been finalized. A review of preliminary data from the elderly cohort showed that following administration of lasmiditan 200 mg, there was a transient elevation in mean supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) between 60 and 90 minutes postdose, with a mean maximum SBP increase of 14.5 mmHg and DBP increase of 3.8 mmHg compared with baseline. Because the number of subjects enrolled in LAHA was based on statistical power to detect differences in PK, it was not possible to determine if the observed effects on blood pressure (BP) were statistically significant. Elderly patients with migraine are among those in the target population for lasmiditan. Therefore, it is important to assess further safety due to the BP response observed in Study LAHA. The current study will test whether each dose level of lasmiditan (100 and 200 mg) is noninferior to placebo with regard to increasing SBP. The intended sample size will have at least 90% power to detect a true mean increase of 5 mmHg in SBP change from baseline between lasmiditan and placebo, assuming a 1-sided significance level of 0.05 and a noninferiority margin of 10 mmHg.

Objective(s)/Endpoints:

Objectives	**Endpoints**
Primary To test whether each oral dose of lasmiditan (100 and 200 mg) is noninferior to placebo with regard to increasing blood pressure in healthy elderly subjects (≥65 years of age).	• Systolic blood pressure obtained via ambulatory blood pressure monitoring (ABPM)
Secondary To determine the PK of lasmiditan in healthy elderly subjects (≥65 years of age) following single 100- and 200-mg oral doses of lasmiditan. To assess the safety and tolerability of 100- and 200-mg oral doses of lasmiditan in healthy elderly subjects.	• PK parameters: maximum observed drug concentration (Cmax), time of Cmax (tmax), and the area under the concentration versus time curve from zero to infinity (AUC[0 ∞]) • A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

Summary of Study Design:

This is a randomized, subject- and investigator-blind, placebo-controlled crossover study with 3 treatment periods to assess BP, PK, and safety and tolerability of 100- and 200-mg oral doses of lasmiditan in healthy elderly subjects. All subjects will participate in 3 treatment periods. The treatments are as follows:

- Treatment A: Lasmiditan 200 mg
- Treatment B: Lasmiditan 100 mg
- Treatment C: Placebo

Each subject will be randomized to 1 of 6 treatment sequences in a Williams design (i.e. ABC, BCA, CAB, CBA, ACB, BAC).

Treatment Arms and Planned Duration for an Individual Subject:
Screening Period:

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

Dosing Period:

All subjects will participate in 3 treatment periods. Subjects will be randomized to 1 of 6 treatment sequences. They will be admitted to the clinical research unit (CRU) the day prior to dosing (Day -1), and receive study drug on Days 1, 3, and 5. Subjects will be discharged from the CRU on Day 7. There will be a washout period of approximately 48 hours between each dosing day. Subjects will remain confined during the entire inpatient period.

Number of Subjects:
Up to 36 subjects may be enrolled to ensure 30 subjects complete the study. Subjects will be aged ≥65 years. Attempts will be made to enroll at least 6 subjects who are aged ≥75 years.

Statistical Analysis:

Cardiovascular parameters that will be assessed using ABPM include peak hourly mean values of SBP. The parameters will be listed, and summarized using descriptive statistics, as appropriate. Changes from baseline in peak hourly mean values of SBP will be analyzed to test whether each dose of lasmiditan (100 and 200 mg) is noninferior to placebo, assuming a noninferiority margin of 10 mmHg. A linear mixed-effects model with baseline as a covariate, fixed effects for treatment, period (1, 2, or 3), and treatment sequence, and a random effect for subject will be used to test the hypotheses at a 1-sided significance level of 0.05. A gatekeeping procedure will be used to adjust for multiplicity when conducting the hypothesis tests comparing lasmiditan 100 mg with placebo and lasmiditan 200 mg with placebo.

Safety parameters that will be assessed include safety laboratory parameters, vital signs, DBP, and pulse rate obtained via ABPM, and adverse events. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameter estimates for lasmiditan will be calculated using standard noncompartmental methods of analysis. The parameters will be listed, and summarized using standard descriptive statistics, including estimates of intra-subject variability as appropriate.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAIG

	Screening	**Inpatient Period**							**Discharge from Clinic or Early Term Procedures**	**Follow up**	**Comments**
Procedure	-28 to -2 days prior to Day 1	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10 ± 2 days	
Informed Consent	X										
C-SSRS and Self Harm Supplement Form	X	X							X	X	For the C-SSRS, use Baseline Version at screening and Since Last Visit Version at all other visits.
Subject Admission to CRU		X									
Subject Discharge from CRU									X		
Randomization			X								Randomization to occur prior to dosing.
Investigational Product Administration			X		X		X				
Medical History	X	X									After screening, medical history should include interim medical history.
AEs and Medication review	X	X	X	X	X	X	X	X	X	X	
Height	X										
Weight	X										
Temperature	X										
Vital Signs (supine)	X	X	Pre-dose and 4 h	24 h	Pre-dose and 4 h	24 h	Pre-dose and 4 h	24 h	X[a]	X	Vital signs will be single measures. The pre-dose measure is taken

											before the ABPM recordings are started. Time points may be added if warranted and agreed upon between Lilly and the investigator.

	Screening	Dosing Period							Discharge from Clinic or Early Term Procedures	Follow up	Comments
Procedure	-28 to -2 days prior to Day 1	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 10 ± 2 days	
Orthostatic Vital Signs	X										
Ambulatory Blood Pressure Monitoring			X		X		X				The ABPM device will be worn for approximately 2 hours before dosing and will continue to be worn until the 24-hour postdose assessment is complete. See Section 9.4.2.1 for details.
ABPM Training		X									Subjects should be trained on the ABPM device on the evening of Day -1. Data from this acclimation period will not be stored or analyzed.
Clinical Laboratory Tests	X	X							X		See Appendix 2, Clinical Laboratory Tests, for details.
Ethanol Test		X									See Appendix 2, Clinical Laboratory Tests, for details.

Urine Drug Screen	X	X									See Appendix 2, Clinical Laboratory Tests, for details.
Physical Examination	X	X		X		X		X	X	X	Full physical examination at screening. Symptom-driven physical examination for all other time points.
12-lead ECG	X		Pre-dose and 4 h	24 h	Pre-dose and 4 h	24 h	Pre-dose and 4 h	24 h			Single ECG readings will be taken. The pre-dose measure is taken before the ABPM recordings are started.
PK Samples			Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	Pre-dose[b], 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	Pre-dose[b], 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48[c]		
Genetic Sample			X								Single sample for pharmacogenetic analysis taken prior to/on Day 1.

Abbreviations: ABPM = ambulatory blood pressure monitoring; AE = adverse event; CRU = clinical research unit; C-SSRS = columbia-suicide severity rating scale; ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

[a] The Day 7 vital sign measurement should be taken approximately 48 hours after the previously administered dose

[b] Pre-dose should be collected approximately 48 hours after the previously administered dose.

[c] Unscheduled PK samples should be drawn for subjects following early termination procedures.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be used: ECG, supine vital signs, and orthostatic vital signs, venipuncture. Where venipuncture and other procedures take place at the same time point, the following time windows for obtaining blood samples should be maintained: >0 to 2 hours postdose: ±5 minutes; 2.5 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes. Where repeats of vital signs measurements are required, repeats should be performed after venipuncture.

3. Introduction

3.1. Study Rationale

Lasmiditan is a small molecule 5-hydroxytryptamine (5-$HT1_F$) receptor agonist being developed for the acute treatment of migraine. Triptans, which are 5-$HT1_B/1_D$ receptor agonists, are well established as an acute therapy for migraine, though they are not effective in all patients or attacks. Triptans were developed as cerebral vasoconstrictors, mediated via their affinity for 5-$HT1_B$ receptors located on vascular smooth muscle. Inherent in this mechanism of action is a liability for coronary vasoconstriction, and therefore, triptans are contraindicated in patients with cardiovascular disease. Unlike triptans, lasmiditan is a highly selective and potent agonist at the 5-$HT1_F$ receptor with >470-fold higher affinity for the 5-$HT1_F$ receptor than for 5-$HT1_B/1_D$ receptors. Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

The prevalence of migraine declines in the population older than 50 years of age; however, 5% to 10% of the population older than 65 years of age still report suffering from migraine (Victor et al. 2010). Thus, elderly patients are anticipated to receive lasmiditan.

Study H8H-MC-LAHA (LAHA) was recently conducted to determine the pharmacokinetics (PK) and safety of lasmiditan in elderly and young healthy subjects following a single oral administration of lasmiditan 200 mg. The study database has been locked but the clinical study report has not been finalized. A review of preliminary data from the elderly cohort showed that following administration of lasmiditan 200 mg, there was a transient elevation in mean supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) between 60 and 90 minutes postdose, with a mean maximum increase in SBP of 14.5 mmHg and in DBP of 3.8 mmHg compared to baseline. Since the number of subjects enrolled in LAHA was based on statistical power to detect differences in PK, it was not possible to determine if the observed effects on blood pressure (BP) were statistically significant. Therefore, it is important to assess further safety due to the response of BP observed in Study LAHA. The current study will test whether each dose level of lasmiditan (100 and 200 mg) is noninferior to placebo with regard to increasing SBP. The intended sample size will have at least 90% power to detect a true mean increase of 5 mmHg in change in SBP from baseline between lasmiditan and placebo, assuming a 1-sided significance level of 0.05 and a noninferiority margin of 10 mmHg.

3.2. Background

Across the completed Phase 1, 2, and 3 clinical studies, doses of 0.1 to 400 mg of lasmiditan were evaluated in healthy subjects or patients with migraine. Compared with placebo, the most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) included dizziness, paresthesia, somnolence, fatigue, lethargy, and nausea. A majority of these TEAEs were mild or moderate in severity and none led to subject withdrawal. One patient experienced a serious adverse event (SAE) of dizziness that was moderate in severity (lasmiditan 200 mg) (Färkkilä et al. 2012).

In the thorough QT study in healthy subjects, no clinically significant changes in BP, heart rate, or 12-lead electrocardiogram (ECG) were observed at the 100- or 400-mg single-dose levels.

In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1.5 to 2.5 hours after a single oral dose ranging from 25 to 400 mg, and the geometric mean terminal half-life was approximately 4 hours. Lasmiditan exhibited dose-linear PK. Co-administration of lasmiditan with a high-fat diet led to a delay in median time of maximum observed drug concentration (tmax) value by approximately 1 hour and a modest (~20%) increase in lasmiditan maximum observed drug concentration (Cmax), and area under the concentration versus time curve (AUC) values, relative to that under fasted conditions.

Following oral dosing with lasmiditan, up to 11 metabolites were detected in human plasma and urine, including 3 major metabolites (M7, M8, and M18). These metabolites lacked significant pharmacological activity at the 5 $HT1_F$ 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 to 21 hours.

Preliminary PK results from Study LAHA demonstrated that in elderly subjects, exposure to lasmiditan as measured by AUC from zero to infinity was 26% (90% confidence intervals (CIs) 1.03, 1.55) higher than in young subjects following dosing with 200 mg lasmiditan. There was no statistically significant difference in exposure to lasmiditan based on Cmax. The tmax of lasmiditan was similar between age groups. The geometric mean $t_{1/2}$ was 5.46 and 4.10 hours in elderly and young subjects, respectively.

Preliminary safety data from Study LAHA show that single doses of 200 mg lasmiditan were well tolerated by 18 healthy elderly and 17 healthy young subjects in this study, with no reported deaths, other SAEs, or discontinuations due to adverse events (AEs). The types of TEAEs reported were consistent with previous studies of lasmiditan in healthy subjects. In elderly subjects, postdose there was a transient elevation in mean supine systolic blood pressure (SBP) and diastolic blood pressure (DBP) between 60 and 90 minutes postdose, with a mean maximum SBP increase of 14.5 mmHg and DBP increase of 3.8 mmHg compared with baseline . The changes in supine vital signs were maximal at approximately 1.5 hours postdose and had returned toward baseline values by the time of the assessment at 3 hours postdose. No such changes were noted in elderly subjects receiving placebo or in young subjects receiving lasmiditan. There were no apparent postdose trends in orthostatic vital signs for any age group.

3.3. Benefit/Risk Assessment

The primary objective of this study is to evaluate the cardiovascular effects after single oral 100- and 200-mg doses of lasmiditan in healthy elderly subjects. There is no anticipated therapeutic benefit for the subjects.

Lasmiditan has been generally well tolerated by healthy subjects as single oral doses up to 400 mg. Elderly patients were enrolled in the completed Phase 3 program, for acute treatment of migraine, that tested single oral doses up to 200 mg, where a second dose was permitted within

the same day if migraine relief had not been achieved. In addition, Study LAHA tested 200 mg lasmiditan in 18 elderly subjects.

In completed clinical studies with single lasmiditan oral doses up to 400 mg, the most frequently reported lasmiditan TEAEs included tiredness, drowsiness, dizziness, and paresthesia. A majority of these TEAEs were mild in severity and none led to subject withdrawal. One patient experienced an SAE of dizziness that was moderate in severity (lasmiditan 200 mg). Dosing of lasmiditan in this study will be conducted in an inpatient setting, and subjects will be monitored in the clinical research unit (CRU) for at least 48 hours after each dosing.

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

4. Objectives and Endpoints

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

Table LAIG 1. Objectives and Endpoints

Objectives	Endpoints
Primary To test whether each oral dose of lasmiditan (100 and 200 mg) is noninferior to placebo with regard to increasing blood pressure in healthy elderly subjects (≥65 years of age).	• Systolic blood pressure obtained via ambulatory blood pressure monitoring (ABPM)
Secondary To determine the PK of lasmiditan in healthy elderly subjects (≥65 years of age) following single 100- and 200-mg oral doses of lasmiditan. To assess the safety and tolerability of 100- and 200-mg oral doses of lasmiditan in healthy elderly subjects.	• PK parameters: maximum observed drug concentration (Cmax), time of Cmax (tmax), and the area under the concentration versus time curve from zero to infinity (AUC[0-∞]) • A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

5. Study Design

5.1. Overall Design

This is a randomized, subject- and investigator-blind, crossover study with 3 treatment periods in healthy elderly subjects. The treatments are as follows:

- Treatment A: Lasmiditan 200 mg
- Treatment B: Lasmiditan 100 mg
- Treatment C: Placebo

Each subject will be randomized to 1 of 6 treatment sequences in a Williams design, as outlined in Table 5.1.

Study governance considerations are described in detail in Appendix 3.

Table 5.1. Sequences in Study LAIG

Sequence	Period 1	Period 2	Period 3
1	Lasmiditan 200 mg	Lasmiditan 100 mg	Placebo
2	Lasmiditan 100 mg	Placebo	Lasmiditan 200 mg
3	Placebo	Lasmiditan 200 mg	Lasmiditan 100 mg
4	Placebo	Lasmiditan 100 mg	Lasmiditan 200 mg
5	Lasmiditan 200 mg	Placebo	Lasmiditan 100 mg
6	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo

Screening Period:

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

Dosing Period:

Subjects will participate in 1 inpatient period involving 3 dosing periods. Subjects will be admitted on Day -1 and will be randomized to 1 of 6 treatment sequences to receive lasmiditan or placebo on Days 1, 3, and 5. There will be a washout period of approximately 48 hours between each dosing day. Subjects may be discharged on Day 7 based on investigators' discretion.

All subjects will be discharged from the study approximately 2 days after their final dose of lasmiditan.

5.2. Number of Participants

Up to 36 subjects may be enrolled to ensure 30 subjects complete the study. Subjects will be aged ≥65 years. Attempts will be made to enroll at least 6 subjects who are aged ≥75 years.

Subjects who discontinue from the study prior to completion may be replaced at the discretion of the sponsor.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

A randomized, subject- and investigator-blind, placebo-controlled design is being used to minimize bias on the safety and tolerability objective. A crossover design improves the sensitivity for detecting any safety/tolerability signals in elderly subjects, particularly in relation to vital signs (as described in Section 5.1).

The washout period of approximately 48 h between each dose is adequate based on the half-life of lasmiditan.

The nonclinical and clinical data enable conducting clinical pharmacology studies in elderly healthy subjects. The single-dose design of this study limits exposure of subjects to lasmiditan and is appropriate to address the study objectives.

5.5. Justification for Dose

The upper dose level of 200 mg lasmiditan has been well tolerated in previous studies of healthy subjects and in elderly patients enrolled in the completed Phase 3 program. This dose level is in the therapeutic dose range and is expected to be the highest potential recommended single dose for lasmiditan. A lower dose of 100 mg lasmiditan will also be evaluated in the current study to explore any cardiovascular effect.

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 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, is 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 enrollment (Day 1):

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

[1a] male subjects:

are not required to adhere to contraceptive requirements.

[1b] female subjects:

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

[2] are aged ≥65 years.

[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 investigator 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 (Day 1):

[8] are investigator site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

[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, related compounds, or any components of the formulation.

[12] are persons who have previously received lasmiditan.

[13] have a history of, or ECG findings of, clinically significant bradycardia, heart block, tachy or brady arrhythmias, 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.

[14] have significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study medication; or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable.

[15] show evidence of significant active neuropsychiatric disease (e.g. manic depressive illness, schizophrenia, depression) considered as clinically significant by the investigator.

[16] show a history of central nervous system (CNS) conditions such as strokes, transient ischemic attacks, significant head trauma, seizures, CNS infections, migraines, brain surgery, or any other neurological conditions that, in the opinion of the investigator, increase the risk of participating in the study.

[17] show evidence of active renal disease (e.g. diabetic renal disease, polycystic kidney disease) or estimated glomerular filtration rate <60 mL/min/1.73 m^2.

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

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

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

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

[22] intend to use over-the-counter or prescription medication, dietary supplements, or strong inhibitors or inducers of cytochrome P450 (CYP)1A and CYP3A activities within 14 days prior to dosing of lasmiditan. Exceptions allowable for subjects on a stable dose of hormone replacement therapy, thyroid replacement therapy, prophylactic anti-platelet drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazides, statins, or protein pump inhibitors (PPIs) for at least 3 months prior to admission; medications falling into the exceptions listed above, and/or others that may be considered not to impact study integrity may be allowed following discussion with the Lilly clinical research physician (CRP)/CP or designee.

[23] have donated blood of more than 500 mL within 2 months prior to the screening visit.

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

[25] have a history of syncope, presyncopy, uncontrolled vertigo, postural dizziness, or at risk for falls, as judged to be clinically significant by the investigator.

[26] are unwilling to refrain from tobacco- or nicotine-containing products while in the CRU or are unable to abide by CRU restrictions.

[27] have orthostatic hypotension with or without dizziness and/or syncope at screening (or upon repeat) or a history of it.

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

[29] 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

The use of lasmiditan in elderly patients is anticipated, thus this study will specifically examine the PK, safety, and tolerability in an elderly population. Criterion 2 defines the elderly population for the purposes of this study.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Lasmiditan or placebo will be administered after an overnight fast of at least 8 hours. Subjects will be given a snack prior to bedtime. Subjects will abstain from water 1 hour before and after dosing (except for water given with the dose). Subjects may be permitted to consume a light breakfast (e.g. cereal, toast) at 1 hour postdose at the discretion of the investigator; with the exception of this light breakfast, subjects will remain fasting for 3 hours postdose at which time a meal will be served.

6.3.2. Caffeine, Alcohol, Tobacco, and Grapefruit

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.

Tobacco – Subjects will refrain from using tobacco- or nicotine-containing products while resident at the CRU.

Grapefruit – Subjects will refrain from consuming grapefruit and grapefruit-containing products from 7 days prior to Day 1, and while resident at the CRU.

6.3.3. Activity

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

6.4. Screen Failures

Individuals may be re-screened once. The interval between re-screenings should be at least 1 week. When re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

Investigational products used in this study are shown in Table 7.1.

Tablets of lasmiditan and/or placebo will be administered orally in the fasted state with approximately 240 mL of room temperature water in the morning of Days 1, 3, and 5, while subjects are in a sitting position. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table 7.1. Treatments Administered

Treatment Name	Lasmiditan	Placebo
Dosage Formulation	Film-coated tablet	Film-coated tablet (matching to lasmiditan)
Unit Dose Strength	100-mg tablet	--
Route of Administration	Oral	Oral
Dosing Instructions[a]	1 or 2 x tablet taken in the morning of each dosing day	1 or 2 x tablet taken in the morning of each dosing day

[a] All subjects will receive 2 tablets at each dosing occasion, i.e. 1 x 100-mg tablet plus 1 matching placebo tablet, or 2 x 100 mg tablet, or 2 matching placebo tablets.

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 100 mg of active ingredient and is provided as bulk supply in bottles. Placebo tablets look identical but contain no active ingredient and will be provided in similar bulk bottles.

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

7.2. Method of Treatment Assignment

All subjects will participate in 3 treatment periods. The treatments are as follows:

- Treatment A: Lasmiditan 200 mg
- Treatment B: Lasmiditan 100 mg
- Treatment C: Placebo

Each subject will be randomized to one of 6 treatment sequences in a Williams design (i.e. ABC, BCA, CAB, CBA, ACB, BAC) using a computer-generated allocation schedule.

7.2.1. Selection and Timing of Doses

Subjects will receive study drugs on Days 1, 3, and 5.

The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

7.3. Blinding

This study will be subject- and investigator-blind. The investigator, site staff (except unblinded pharmacy staff), and subjects will be blinded to study treatment.

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

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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

7.4. Dose Modification

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

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

Acetaminophen may be allowed at the investigator's discretion, up to 2 g in a 24-hour period, without prior consultation with the sponsor.

Stable doses of hormone replacement therapy, thyroid replacement therapy, prophylactic antiplatelet drugs, ACE inhibitors, ARBs, thiazides, statins, or PPIs for at least 3 months prior to admission. Medications falling into the exceptions listed above, and/or others that may be considered not to impact study integrity may be allowed following discussion with the Lilly CRP/CP or designee.

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

7.8. Treatment after the End of the Study

This section is not applicable to this study.

8. Discontinuation Criteria

Subjects discontinuing from the study prematurely for any reason must complete adverse event (AE) and discharge procedures per Section 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) >5X upper limit of normal (ULN)
- ALT or AST >3X ULN and total bilirubin >2X ULN or international normalized ratio (INR) >1.5
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- alkaline phosphatase (ALP) >3X ULN
- ALP >2.5X ULN and total bilirubin >2X ULN
- ALP >2.5X 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 CP/CRP or designee and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP or designee to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

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

- Subject Decision
    - the subject, or legal representative, 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 laboratory tests that will be performed for this study.

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

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

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e. 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 patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

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

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

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

Pregnancy (maternal or paternal exposure to 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 lasmiditan 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 dose assigned through randomization. There is no specific antidote for lasmiditan. In the event of overdose, the subject should receive appropriate supportive care and AEs should be documented.

Refer to the IB.

9.4. Safety

9.4.1. Laboratory Tests

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

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

9.4.2. Vital Signs

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

Blood pressure and pulse rate (PR) should be measured singly after at least 5 minutes supine. For each individual subject, the same cuff size should be used throughout the study for the measurements of BP. The cuff should be attached to the subject's dominant arm (nondominant arm will be used for ambulatory blood pressure monitoring [ABPM]).

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

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

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

9.4.2.1. Ambulatory Blood Pressure Monitoring

For each subject, ABPM will be performed according to the Schedule of Activities (Section 2).

Site investigative personnel should be trained on the correct positioning of the ABPM monitor, use of correct cuff size, and monitor calibration prior to the start of the study. Subjects should be trained on the ABPM device on the evening of Day -1 to maximize the collection of valid measurements, and to alleviate any concerns about inconvenience due to the continuous 24-hour monitoring.

The ABPM device should be attached to the subject's nondominant arm and will record ambulatory BP and PR every 20 minutes during awake hours (e.g. 0700 hours to 2200 hours) and every 30 minutes throughout the night (2200 hours to 0700 hours). On Days 1, 3, and 5 when dosing occurs, the BP and PR recording will be initiated approximately 2 hours prior to the planned dosing time and will continue for approximately 26 hours. Subjects will be encouraged to keep the same routine without strenuous activity during the ABPM recording days.

The ABPM device should be removed from each subject prior to their discharge from the CRU.

9.4.3. Electrocardiograms

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

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

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). 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. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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

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

9.4.4. Safety Monitoring

The Lilly CP 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 CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes
- adverse events.

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

9.4.4.1. Hepatic Safety

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

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

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

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

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 will be assayed using a validated liquid chromatography with tandem mass spectrometry method. Analyses of samples collected from subjects who received placebo are not planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study.

9.6. Pharmacodynamics

This section is not applicable for this study.

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 36 subjects may be enrolled to ensure 30 subjects complete the study. Assuming a 1-sided significance level of 0.05, a standard deviation for the within-subject change in SBP of 6.0 mmHg (a slightly larger estimate than that seen in Study LAHA), and a noninferiority margin of 10 mmHg, this sample size will result in at least 90% power to detect a true increase of 5 mmHg in the mean within-subject change for lasmiditan 200 mg compared with placebo.

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.

Cardiovascular analyses will be conducted on data from subjects who complete at least 1 dosing period.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational products and have evaluable PK.

Pharmacokinetic/pharmacodynamic analyses will be conducted on data from subjects who have evaluable data in both PK and cardiovascular datasets.

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.

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 Dictionary for Regulatory Activities.

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

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, DBP, and pulse rate obtained via ABPM, and AEs. The 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 will be calculated using standard noncompartmental methods of analysis. The primary parameters for analysis will be C_{max} and AUC of lasmiditan. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Analysis

The parameters will be listed, and summarized using standard descriptive statistics, including estimates of intra-subject variability as appropriate.

10.3.3. Cardiovascular Analyses

10.3.3.1. Cardiovascular Parameter Estimation

The primary parameters for the cardiovascular analyses will be peak hourly mean values of SBP, and will be determined using ABPM. For each subject, the mean SBP will be calculated for each hour within the dosing period. The highest mean value across the 24 calculated means will be considered the peak hourly mean value. Baseline value will be defined as the mean value during the 2 hours pre-dose for each period.

10.3.3.2. Statistical Inference of Cardiovascular Parameters

Cardiovascular parameters will be listed, and summarized using descriptive statistics, as appropriate.

As a primary analysis, changes from baseline in peak hourly mean values of SBP will be analyzed to test whether each dose of lasmiditan (100 mg, 200 mg) is noninferior to placebo, assuming a noninferiority margin of 10 mmHg. Specifically, these changes from baseline will be analyzed to test the null hypotheses that the difference in mean baseline change between lasmiditan at each dose and placebo is at least 10 mmHg versus the alternative hypotheses that this difference is less than 10 mmHg.

A linear mixed-effects model with baseline as a covariate, fixed effects for treatment, period (1, 2, or 3), and treatment sequence, and a random effect for subject will be used to test the hypotheses at a 1-sided significance level of 0.05. Least squares (LS) means and treatment

differences (lasmiditan 200 mg – placebo, lasmiditan 100 mg - placebo) will be calculated and presented with their corresponding 95% CIs.

The following gatekeeping procedure will be used to adjust for multiplicity when conducting the hypothesis tests. The null hypothesis that the difference in mean baseline change between lasmiditan 100 mg and placebo is at least 10 mmHg will first be tested against the alternative hypothesis that this difference is less than 10 mmHg. If the p-value for this test is less than 0.05, then there is significant evidence that lasmiditan 100 mg is non-inferior to placebo and these hypotheses will be re-tested using lasmiditan 200 mg. Otherwise, if the p-value is at least 0.05, then there is no significant evidence that lasmiditan 100 mg is noninferior to placebo, in which case the null and alternative hypotheses will not be re-tested using lasmiditan 200 mg.

A sensitivity analysis will be performed on subjects who complete all 3 dosing periods. The same mixed-effects model as that was used in the primary analysis will be implemented.

A repeated measures analysis will also be conducted in which changes from baseline in hourly mean values of SBP will be analyzed to test whether each dose of lasmiditan (100 mg, 200 mg) is noninferior to placebo at each time point (hour), assuming a noninferiority margin of 10 mmHg. A repeated measures linear mixed-effects model with baseline as a covariate, fixed effects for time point, treatment, period, treatment sequence, and the treatment by time point interaction, and a random effect for subject will be used to conduct the tests at a 1-sided significance level of 0.05. At each time point, LS means and treatment differences (lasmiditan 200 mg – placebo, lasmiditan 100 mg – placebo) will be calculated and presented with their corresponding 95% CIs, from which noninferiority of lasmiditan (100 mg, 200 mg) to placebo will be determined if the upper confidence limit is less than 10 mmHg.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

The relationship between PK and cardiovascular effects will be explored initially in a graphical manner. Additional modeling approaches or graphical analyses may be used, if warranted.

10.3.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, 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

Färkkilä M, Diener HC, Géraud G, Láinez M, Schoenen J, Harner N, Pilgrim A, Reuter U; COL MIG-202 Study Group. Efficacy and tolerability of lasmiditan, an oral 5-HT(1F) receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol*. 2012;11(5):405-413.

Victor TW, Hu X, Campbell JC, Buse DC, Lipton RB. Migraine prevalence by age and sex in the United States: a life span study. *Cephalalgia*. 2010;30(9):1065-1072.

Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARB	angiotensin receptor blocker
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CI	confidence interval
Cmax	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 re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
CYP	cytochrome P450
DBP	diastolic blood pressure
eCRF	electronic case report form
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.
ERB	ethical review board
GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
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	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.
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
LS	least squares

PK	pharmacokinetic(s)
PPI	protein pump inhibitor
PR	pulse rate
randomize	The process of assigning subjects/patients to an experimental group on a random basis.
SAE	serious adverse event
SBP	systolic blood pressure
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.
SUSAR	suspected unexpected serious adverse reaction
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
tmax	time of maximum observed drug concentration
ULN	upper limit of normal

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/or % of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
Urinalysis	Creatinine
Specific gravity	Ethanol testing[a]
pH	Urine drug screen[a,b]
Protein	Hepatitis B surface antigen[b]
Glucose	Hepatitis C antibody[b]
Ketones	HIV[b]
Bilirubin	FSH[c]
Urobilinogen	
Blood	
Nitrite	
Leukocytes	
Urine microscopic (if positive result for blood)	

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

[a] Performed on admission.

[b] Performed at screening.

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

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 Harmonization (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 International Ethical Guidelines
2) applicable ICH GCP Guidelines

3) applicable laws and regulations

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

Protocol Signatures

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

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

Final Report Signature

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

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

Data Quality Assurance

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

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

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

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

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol H8H-MC-LAIG 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	2	25
Pharmacokinetics	2	40	80
Pharmacogenetics	10	1	10
Total			134.5
Total for clinical purposes rounded up to the nearest 10 mL			140

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

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