Protocol H8H-MC-LAHA (a)

Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects

NCT03182920

Approval Date: 05-Jul-2017

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Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects

Lasmiditan (LY573144)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 27 April 2017.
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 05-Jul-2017 GMT

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1. Protocol Synopsis

Title of Study:
Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects

Objectives/Endpoints:

Objectives	Endpoints
Primary To determine the pharmacokinetics (PK) of lasmiditan in healthy elderly subjects (≥65 years of age) following a single 200 mg oral dose of lasmiditan.	• PK parameters: maximum observed concentration (C_{max}), time of C_{max} (t_{max}), and the area under the concentration versus time curve from zero to infinity (AUC[0-∞])
Secondary To compare the PK of lasmiditan in healthy elderly subjects (≥65 years of age) against the PK of lasmiditan in healthy young subjects (18 to 45 years of age) following a single 200 mg oral dose of lasmiditan. To assess the safety and tolerability of a single 200 mg oral dose of lasmiditan in elderly and young healthy subjects.	• PK parameters: C_{max}, t_{max}, and AUC(0-∞) • A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Exploratory To determine the PK of the metabolites M8, M7, and M18 in healthy elderly and young subjects following a single 200 mg oral dose of lasmiditan.	• PK parameters: C_{max}, t_{max}, and AUC(0-∞)

Summary of Study Design:

This is a single dose study to determine the PK of lasmiditan following a single 200 mg oral dose in healthy elderly and young subjects. Two groups of subjects will be studied as follows:

Group 1 (healthy elderly subjects): 200 mg lasmiditan and matching placebo in a randomized double-blind cross-over design

Group 2 (healthy young subjects): 200 mg lasmiditan in an open label design

Subjects in Group 2 will be matched by race, sex, and body mass index (BMI) (±20%) to subjects in Group 1. Both groups may be evaluated concurrently.

Treatment Arms and Duration:

Screening Period:

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

Dosing Period:

Subjects in Group 1 will participate in 2 dosing periods. Subjects will be randomized to receive lasmiditan in one dosing period, and placebo in the other. They will be admitted to the CRU the day prior to dosing (Day -1), and receive study drug on Day 1 for each dosing period. Subjects may be discharged from the CRU on Day 3 based on investigator discretion. There will be a washout period of 3 to 10 days between each dosing day. Subjects may stay as inpatient during the entire dosing period.

Subjects in Group 2 will participate in 1 dosing period. They will be admitted to the CRU on Day -1 and receive study drug on Day 1. Subjects may be discharged from the CRU on Day 3 based on investigator discretion.

All subjects will be discharged from the study approximately 7 days post their final dose of lasmiditan.

Number of Subjects:

Up to 36 subjects may be enrolled to ensure 30 subjects (2 groups of 15) complete the study. Group 1 will be subjects aged ≥65 years of age. Attempts will be made to enroll at least 4 subjects who are ≥75 years of age. Group 2 will be subjects aged 18 to 45 years, inclusive.

Statistical Analysis:

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and 12-lead electrocardiogram (ECG) parameters. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameter estimates for lasmiditan and its metabolites will be calculated by standard noncompartmental methods of analysis. Pharmacokinetic parameter estimates will be evaluated to determine the impact of age on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC(0-∞) will be evaluated in a linear fixed-effects model with a fixed effect of age group. The 90% confidence intervals (CIs) of the ratios of geometric means of the elderly group versus the young group will be presented.

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 the p-value from the Wilcoxon test will be calculated.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHA (a)

	Screening	Periods 1 and 2[a]				Discharge from Study/ Early Discontinuation	Comments
Procedure	-28 to -2 days prior to Day 1	Day -1[b]	Day 1	Day 2	Day 3	approximately 7 days post final dose	
Informed Consent	X						
Subject Admission to CRU		X					
Subject Discharge from CRU					X[c]		
Randomization			Predose[d]				
Investigational Product Administration			Day 1, indicates Time = 0				
Medical History	X						
AEs and Medication review		X	X	X	X	X	
Height	X						
Weight	X						
Temperature	X						
Vital Signs (supine)	X		Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24	48	X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator. All assessments except for screening should be performed in triplicate. See Section 9.4.2 for further details.

Study Schedule Protocol H8H-MC-LAHA

	Screening	Periods 1 and 2[a]				Discharge from Study/ Early Discontinuation	Comments
Procedure	-28 to -2 days prior to Day 1	Day -1[b]	Day 1	Day 2	Day 3	approximately 7 days post final dose	
Orthostatic Vital Signs	X	X	Predose, 0.5, 1, 2	24			Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes, where applicable. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Screening laboratory Tests	X						
Clinical Lab Tests	X	X	Predose		X	X	See Appendix 2, Clinical Laboratory Tests, for details.
Urine Drug Screen and alcohol screen	X	X[e]					
Pregnancy Test	X	X				X	Serum pregnancy test will be performed at all time points.
Physical Exam		X	X	X	X	X	Full physical examination at Day -1 of each study period (as applicable for Group 1) and discharge from the study only. Symptom driven physical examination for all other timepoints.
12-lead ECG	X	X	Predose, 1, 2, 4 hours postdose	24 hours postdose		X	Single ECG readings will be taken.
PK Samples			Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4,	24, 36	48		Sampling times are relative to the time of study treatment administration (0 min).

			6, 8, 12				
Genetic Sample			X				Single sample for pharmacogenetic analysis taken prior to/on Day 1

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

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; >6 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.

[a] Only subjects in Group 1 (elderly subjects) will participate in Period 2.

[b] To be repeated for all subjects in Group 1 ahead of participation in Period 2.

[c] For Group 1 patients who complete Period 1 and will remain inpatient through Period 2, CRU discharge will occur after completion of Period 2.

[d] Group 1 (elderly subjects) only.

[e] Not required at Period 2 for subjects in Group 1 who are not discharged between treatment periods.

3. Introduction

3.1. Study Rationale

Lasmiditan is a small molecule 5-HT1F receptor agonist being developed for the acute treatment of migraine. Triptans, which are 5-HT1B/1D receptor agonists, are well established as an acute therapy for migraine, though they are not effective in all patients or attacks. Triptans were developed as cerebral vasoconstrictors, mediated via their affinity for 5-HT1B receptors located on vascular smooth muscle. Inherent in this mechanism of action is a liability for coronary vasoconstriction, and therefore, triptans are contraindicated in patients with cardiovascular disease. Unlike triptans, lasmiditan is a highly selective and potent agonist at the 5-HT1F receptor with >470-fold higher affinity for the 5-HT1F receptor than for 5-HT1B/1D receptors. Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

While the prevalence of migraine declines in population older than 50 years of age, between 5-10% of population older than 65 still suffer from migraine (Victor et al. 2010). Elderly patients are among those in the target population for lasmiditan.

The present clinical study is being conducted to determine the PK of lasmiditan in elderly and young healthy subjects following a single oral administration of lasmiditan.

3.2. Background

Two Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine, using doses of up to 45 mg over 20 minutes of the intravenous (IV) 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 most relief of bothersome migraine symptoms (nausea, phonophobia, and photophobia) compared to placebo.

Five Phase 1 studies of lasmiditan have been completed and methods of administration included IV, oral, and sublingual. Single doses of lasmiditan were tolerated by healthy subjects when administered IV up to 180 mg over 60 minutes (H8H-MC-LAHA; 40 subjects), as solution formulations administered orally or sublingually up to doses of 400 and 32 mg, respectively (COL MIG-102; 60 subjects), as oral tablets or a solution formulation up to doses of 400 and 200 mg, respectively (COL MIG-103; 44 subjects), and as oral tablets up to 200 mg (COL MIG-104; 30 subjects) and 400 mg (COL MIG-105; 55 subjects).

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. To date, lasmiditan has been administered to 213 healthy subjects, and to 1632 patients with migraine. In the SAMURAI study, 1239 patients aged 18 to 79 years received at least 1 dose of lasmiditan. No PK data were obtained in this study, and by-age analyses of safety data have not been completed. Compared with placebo, the most frequently reported lasmiditan treatment emergent adverse events

(TEAEs) included somnolence, fatigue, dizziness, paresthesia, and hot flashes. The majority of these TEAEs were mild or moderate in severity and none led to subject withdrawal. One subject experienced an SAE of dizziness that was moderate in severity (lasmiditan 200 mg).

When administered intravenously at the highest dose of 180 mg (H8H-MC-LAHA), lasmiditan produced a statistically significant but small 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.

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

In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1 to 2.5 hours after a single oral dose, and the geometric mean terminal half-life was approximately 4 to 6 hours. Lasmiditan exhibited dose-linear pharmacokinetics with low to moderate inter-subject variability in exposure (AUC %CV ranged from 14 to 45%; COL MIG-102) after oral dose administration. Renal clearance of lasmiditan was low with approximately 2% of the dose recovered by 24 hours postdose. Co-administration of lasmiditan with a high fat diet led to a delay in median t_{max} value by approximately 1 hour and a modest (~20%) increase in lasmiditan C_{max} and AUC values, relative to that under fasted conditions. Based on the short terminal half-life observed following a single oral dose, accumulation of lasmiditan is not expected. There are currently no PK data from elderly subjects available from the completed or ongoing trials.

Human metabolism has been investigated using 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 were approximately linear. The half-life of the metabolites ranged from ~4.5 hours to >12 hours.

3.3. Benefit/Risk Assessment

The primary objective for this study is to evaluate the PK profile of lasmiditan after a single oral dose in healthy elderly and young subjects. There is no anticipated therapeutic benefit for the subjects.

Lasmiditan has been well tolerated by healthy subjects as single oral doses up to 400 mg. Elderly patients were enrolled in the completed Phase 3 program (SAMURAI) for acute

migraine treatment that tested single doses up to 200 mg, where a second dose was permitted within the same day if migraine relief had not been achieved.. 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.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of lasmiditan are to be found in the IB.

4. Objectives and Endpoints

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

Table LAHA.1. Objectives and Endpoints

Objectives	Endpoints
Primary To determine the pharmacokinetics (PK) of lasmiditan in healthy elderly subjects (≥65 years of age) following a single 200 mg oral dose of lasmiditan.	• PK parameters: C_{max}, t_{max}, and AUC(0-∞)
Secondary To compare the PK of lasmiditan in healthy elderly subjects (≥65 years of age) against the PK of lasmiditan in healthy young subjects (18 to 45 years of age) following a single 200 mg oral dose of lasmiditan. To assess the safety and tolerability of a single 200 mg oral dose of lasmiditan in elderly and young healthy subjects.	• PK parameters: C_{max}, t_{max}, and AUC(0-∞) • A summary of the number of treatment-emergent AEs (TEAEs) and SAEs
Exploratory To determine the PK of the metabolites M8, M7, and M18 in healthy elderly and young subjects following a single 200 mg oral dose of lasmiditan.	• PK parameters: C_{max}, t_{max}, and AUC(0-∞)

5. Study Design

5.1. Overall Design

This is a single dose study to determine the PK of lasmiditan following a single 200 mg oral dose in healthy elderly and young subjects. Two groups of subjects will be evaluated as follows:

- Group 1 (healthy elderly subjects; ≥65 years): 200 mg lasmiditan and placebo in a randomized, double-blind, 2-period crossover design
- Group 2 (healthy young subjects; 18 to 45 years, inclusive): 200 mg lasmiditan in an open label design

Subjects in Group 2 will be matched by primary race, sex, and BMI (±20%) to subjects in Group 1 where feasible. Both groups may be studied concurrently.

Screening Period:

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

Dosing Period:

Subjects in Group 1 will participate in 2 dosing periods. They will be admitted to the CRU on the day prior to dosing (Day -1), and receive study drug on Day 1 for each dosing period. Subjects may be discharged from the CRU on Day 3 based on investigator discretion. There will be a washout period of 3 to 10 days between each dose. Subjects may stay in the CRU as inpatient during the entire dosing period.

Subjects in Group 2 will participate in 1 dosing period. They will be admitted to the CRU on Day -1 and receive study drug on Day 1. Subjects may be discharged from the CRU on Day 3 based on investigator discretion.

All subjects will be discharged from the study approximately 7 days post their final dose of lasmiditan.

5.2. Number of Participants

Up to 36 subjects may be enrolled to ensure 30 subjects (2 groups of 15) complete the study. Group 1 will be subjects aged ≥65 years of age. Attempts will be made to enroll at least 4 subjects who are ≥75 years of age. Group 2 will be young subjects aged 18 to 45 years, inclusive. Subjects who discontinue from the study prior to completion may be replaced.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

A subject- and investigator-blinded, randomized and placebo controlled design is being used for Group 1, to minimize bias on the safety and tolerability objective for this group. A crossover

design improves the sensitivity for detecting any safety / tolerability signals in the elderly subjects, particularly in relation to vital signs (as described in Section 3.2). Lasmiditan administered by IV infusion has been generally well tolerated by healthy subjects, with most AEs being mild in intensity at all dose levels, but there was a dose-related increase in the number of moderate AEs. The most frequently reported AEs following IV administration in healthy subjects were nervous system related (tiredness, drowsiness, dizziness, somnolence, fatigue, and paresthesia). The AE profile of orally administered lasmiditan in healthy subjects was qualitatively similar to that observed in the IV study. At the highest dose of 400 mg, most AEs were mild in severity and none were severe.

A minimal duration for the washout period is 3 days, which is adequate based on the half-life of lasmiditan.

An open label design is being used for Group 2, as the key objective for this group is based on PK, which is not subject to bias.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

The nonclinical and clinical data enable conducting clinical pharmacology studies in young and 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 dose level of 200 mg lasmiditan has been well tolerated in previous studies of healthy subjects and in elderly patients enrolled in the SAMURAI study. This dose level is in the therapeutic dose range and is expected to be the highest potential recommended single dose for lasmiditan.

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 electrocardiogram (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, 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 enrollment (Day 1):

[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 3 months following the dose of lasmiditan. Reliable methods of contraception for female subjects of childbearing potential include the use of stable oral, implanted, or injected contraceptive hormones, bilateral tubal ligation, intrauterine device, or diaphragm with spermicide along with male partner's use of male condom with spermicide.

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

[2] For Group 1, subjects must be aged ≥65 years, and Group 2, subjects must be aged between 18 and 45 years, inclusive.

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

[4] have clinical laboratory test results within normal reference range for the population or 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 the investigational product in this study, withdrawn from this study or any other study investigating lasmiditan.

[13] have an 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 (for example, manic depressive illness, schizophrenia, depression).

[16] have an increased risk of seizures based on a history of:

- one or more seizures;
- head trauma with loss of consciousness or a post-concussive syndrome or lifetime history of head trauma with persistent neurological deficit (focal or diffuse);

- active CNS infection, uncontrolled migraine or transient ischemic attack (TIA); stroke with persistent neurological deficit (focal or diffuse). Uncontrolled migraine is defined as migraine attacks that produce headache lasting up to 72 hours and are often accompanied by associated symptoms (nausea, photophobia, and phonophobia) that impair well-being and disrupt social functioning. TIA is defined as "mini-stroke" caused by temporary disturbance of blood supply to an area of the brain, which results in a sudden, brief decrease in brain function;
- CNS infection with persistent neurological deficit (focal or diffuse);
- brain surgery;
- electroencephalogram (EEG) with paroxysmal (epileptiform) activity (isolated spikes waves, repetitive bursts of sharp waves, paroxysmal activity, frank seizures, spike-wave complexes, or sharp-slow wave complexes, or as locally defined);
- brain structural lesion, including developmental abnormalities, as determined by examination or imaging studies (except hydrocephalus treated by shunt and without neurological deficit).

[17] show evidence of active renal disease (for example, diabetic renal disease, polycystic kidney disease) or estimated glomerular filtration rate (eGFR) <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] are women with a positive pregnancy test or women who are lactating.

[23] intend to use over-the-counter or prescription medication, dietary supplements or strong inhibitors or inducers of CYP1A and CYP3A activities within 14 days prior to dosing of lasmiditan (except for those described in criterion 1b and Section 7.7). For group 1 (elderly), 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; 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.

[24] subjects on any anti-arrhythmic medications, or medications that could significantly affect QTc intervals.

[25] have donated blood of more than 500 mL within 3 months prior to the screening visit.

[26] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), or are unwilling to stop alcohol consumption 48 hours prior to admission and whilst resident at the CRU (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).

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

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

[29] have ECG findings or clinically significant bradycardia, cardiac block, tachy or brady arrhythmias.

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

[31] have orthostatic hypotension with or without dizziness and/or syncope at screening or Day -1 upon repeat testing, or a history of it.

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 (Group 1). Criteria 2 and 17 define the elderly population for the purposes of this study. Therefore, subjects meeting the elderly criteria are excluded from Group 2.

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, 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.

Tobacco – Subjects will refrain from smoking while resident at the CRU.

6.3.3. Activity

No strenuous exercise will be allowed for 48 hours prior to admission until after discharge from the study.

6.4. Screen Failures

Individuals being recruited into Group 1 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.

Individuals being recruited into Group 2 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 LAHA.2.

Tablets of lasmiditan or placebo will be administered orally in the fasted state with approximately 240 mL of room temperature water in the morning of Day 1 of each period (where applicable), 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 LAHA.2. Treatments Administered

Treatment Name	lasmiditan	Placebo
Dosage Formulation	film-coated tablet	film-coated tablet (matching to lasmiditan)
Unit Dose Strength[a]	(1 × 200-mg) tablet or (2 × 100-mg) tablets/ 200 mg lasmiditan	--
Route of Administration	Oral	Oral
Dosing Instructions[a]	1 or 2 x tablet taken in the morning of Day 1	1 or 2 x tablet taken in the morning of Day 1

[a] All subjects will receive the same number of tablets at each dosing occasion, i.e. 1 × 200-mg OR 2 × 100-mg tablets or 1 or 2 matching placebos. Whether subjects will receive 1 OR 2 tablets will be determined prior to study start.

The investigator or designee is responsible for:

- explaining the correct use of the investigational product 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 or 200 mg of active ingredient and is provided as bulk supply in bottles. Placebo tablets look identical but contain no active ingredient and will be provided in similar bulk bottles.

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

7.2. Method of Treatment Assignment

Subjects in Group 1 will be randomized to 1 of 2 treatment sequences (lasmiditan in Period 1 and placebo in Period 2; or placebo in Period 1 and lasmiditan in Period 2) using a computer-generated allocation schedule.

All subjects in Group 2 will receive the same treatment and will not be subject to randomization.

7.2.1. Selection and Timing of Doses

On Day 1, subjects will receive a single oral dose of 200 mg lasmiditan (Group 1 and 2) or placebo (Group 1 only).

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

7.3. Blinding

Group 1 will be subject- and investigator-blind. For this group, the investigator, site staff (except unblinded pharmacy staff), and subjects will be blinded to study treatment.

Group 2 will be open-label.

Emergency codes for Group 1 will be available to the investigator. A code, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

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

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

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

7.4. Dose Modification

Dose modification 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.

Contraceptive medication is permitted as outlined in Inclusion Criterion 1b. For subjects in group 1 (elderly), hormone replacement therapy, thyroid replacement therapy, prophylactic anti-platelet drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazides, statins, and proton pump inhibitors (PPIs) may be permitted following discussion with the Lilly CRP/CP, or designee.

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

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

7.8. Treatment After the End of the Study

This section is not applicable to this study.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

Subjects discontinuing from the investigational product prematurely for any reason must complete adverse event and discharge procedures per Section 2 of this protocol.

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 patient 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 patient 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, 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 4 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 CRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the 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 patient or may require intervention to prevent one of the other outcomes listed in the definition above.

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

All AEs occurring after signing the ICF are recorded in the case report forms and assessed for serious criteria. The SAE reporting to the sponsor begins after the subject has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

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 [IP]) does not meet the definition of an adverse event. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

Subjects should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP so that the situation can be assessed.

9.3. Treatment of Overdose

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

No drug interaction studies in humans have yet been performed with lasmiditan.

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

9.4.2. Vital Signs

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

Blood pressure and pulse rate should be measured after at least 5 minutes supine. Elderly subjects may be permitted to lie in a semi-recumbent position, if required. All supine/semi-recumbent blood pressure and pulse rate except for screening will be done in triplicates at approximately 1-minute intervals. Where applicable, the last triplicate vital sign can be used as the supine/semi-recumbent vital sign for the calculation of orthostatic changes.

Where orthostatic measurements are required, subjects should be supine/semi-recumbent for at least 5 minutes and stand for at least 2 minutes.

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

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

9.4.3. Electrocardiograms

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

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

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

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

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

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

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, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly clinical pharmacologist or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

- elevation of serum ALT to ≥ 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, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan and metabolites.

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.

Plasma concentrations of lasmiditan and three major metabolites will be assayed using a validated LC/MS/MS method.

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

Bioanalytical samples collected to measure lasmiditan and metabolite 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 mandatory blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations allow.

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

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of lasmiditan or after lasmiditan is commercially available.

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

9.8. 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 in order that 30 subjects (2 groups of 15) complete the study.

For AUC or Cmax, assuming inter-subject CV of 40% and a sample size of 15 per group, the 90% confidence interval around the ratio of the geometric means (elderly group : non-elderly group) will have half-width of 24.3% on the log scale with 90% coverage probability.

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 one dose of the IP and have evaluable PK.

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.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, and ECG parameters. The parameters will be listed and summarized using standard descriptive

statistics, as appropriate. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan and its metabolites will be calculated by standard noncompartmental methods of analysis and will be listed and summarized for each group of subjects using descriptive statistics.

The primary parameters for analysis will be maximum drug concentration (C_{max}) and area under the concentration versus time curve (AUC) from zero to infinity (AUC[0-∞]), and the time of maximum drug concentration (t_{max}) of lasmiditan and its metabolites. 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 parameter estimates will be evaluated to determine the impact of age on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC(0-∞) will be evaluated in a linear fixed-effects model with a fixed effect of age group. The 90% CIs of the ratios of geometric means of the elderly group versus the young group will be presented.

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 the p-value from the Wilcoxon test will be calculated.

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

10.3.3. 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

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

Appendix 1. Abbreviations and Definitions

Term	Definition
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.
ARB	angiotensin receptor blocker
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
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.
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.
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
GCP	good clinical practice
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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product	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.
Non-investigational product	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.
PPI	protein pump inhibitor
randomize	the process of assigning subjects/patients 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
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

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	Urine drug and alcohol screen
Ketones	Hepatitis B surface antigen[a]
Bilirubin	Hepatitis C antibody[a]
Urobilinogen	HIV[a]
Blood	Serum Pregnancy test
Nitrite	FSH[b]
Urine microscopic[c]	Thyroid stimulating hormone[d]

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

[a] Screening only

[b] Screening only for confirmation of post-menopausal status.

[c] Test only if dipstick result is abnormal and per investigator's discretion.

[d] Per investigator's discretion.

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 IP.
- 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 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 sites. Lilly or its representatives must approve the ICF before it is used at the investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

The study sites' 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 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 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**
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, safety laboratories, and bioanalytical assays) during the study.

Protocol H8H-MC-LAHA Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests	8	8[b]/5[c]	64[b]/40[c]
Serum pregnancy test	5	4[b]/3[c]	20[b]/15[c]
Pharmacokinetics	2	28[b]/ 14[c]	56[b]/28[c]
Pharmacogenetics	10	1	10
Total			195[b]/138[c]
Total for clinical purposes rounded up to nearest 10 mL			200[b]/140[c]

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

b Group 1.

c Group 2.

Appendix 6. Protocol Amendment H8H-MC-LAHA (a) Summary: Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects

Overview

Protocol H8H-MC-LAHA, Effect of Age on the Pharmacokinetics, Safety, and Tolerability of Lasmiditan in Healthy Subjects, 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.

Changes were made to the protocol based on feedback from the investigative staff. Specifically, edits were made to clarify the schedule of assessments, the exclusion criteria, concomitant medication specifications, data protection, and the clinical laboratory test parameters.

Revised Protocol Sections

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

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHA

	Screening	**Periods 1 and 2[a]**				**Discharge from Study/ Early Discontinuation**	**Comments**
Procedure	-28 to -2 days prior to Day 1	Day -1[b]	Day 1	Day 2	Day 3	approximately 7 days post final dose	
Informed Consent	X						
Subject Admission to CRU		X					
Subject Discharge from CRU					X[c]		
Randomization			Predose[d]				
Investigational Product Administration			Day 1, indicates Time = 0				
Medical History	X						
AEs and Medication review		X	X	X	X	X	
Height	X						
Weight	X						
Temperature	X						
Vital Signs (supine)	X		Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24	48	X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator. All assessments except for screening should be performed in triplicate. See Section 0 for further details.

Study Schedule Protocol H8H-MC-LAHA

	Screening	Periods 1 and 2[a]				Discharge from Study/ Early Discontinuation	Comments
Procedure	-28 to -2 days prior to Day 1	Day -1[b]	Day 1	Day 2	Day 3	approximately 7 days post final dose	
Orthostatic Vital Signs	X	X	Predose, 0.5, 1, 2	24			Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes, where applicable. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Screening laboratory Tests	X						
Clinical Lab Tests	X	X	Predose		X	X	See Appendix 2, Clinical Laboratory Tests, for details.
Urine Drug Screen and alcohol screen	X	X[e]					
Pregnancy Test	X	X				X	Serum pregnancy test will be performed at all time points.
Physical Exam		X	X	X	X	X	Full physical examination at Day -1 of each study period (as applicable for Group 1) and discharge from the study ~~visit~~ only. Symptom driven physical examination for all other timepoints.
12-lead ECG	X	X	Predose, 1, 2, 4 hours postdose	24 hours postdose		X	Single ECG readings will be taken.
PK Samples			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).

Genetic Sample			X				Single sample for pharmacogenetic analysis taken prior to/on Day 1

Abbreviations: AE = adverse event; CRU = clinical research unit; ECG = electrocardiogram; min = minutes; PK = pharmacokinetics.

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; ~~3~~ 2.5 to 6 hours postdose: ±10 minutes; ~~7~~>6 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.

[a] Only subjects in Group 1 (elderly subjects) will participate in Period 2.

[b] To be repeated for all subjects in Group 1 ahead of participation in Period 2.

[c] For Group 1 patients who complete Period 1 and will remain inpatient through Period 2, CRU discharge will occur after completion of Period 2.

[d] Group 1 (elderly subjects) only.

[e] Not required at Period 2 for subjects in Group 1 who are not discharged between treatment periods.

6.2. Exclusion Criteria

[23] intend to use over-the-counter or prescription medication, dietary supplements or strong inhibitors or inducers of CYP1A and CYP3A activities within 14 days prior to dosing of lasmiditan (except for those described in criterion 1b and Section 7.7). For group 1 (elderly), 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; 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.

[26] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), or are unwilling to stop alcohol consumption 48 hours prior to admission and whilst resident at the CRU~~dosing 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).

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.

Contraceptive medication is permitted as outlined in Inclusion Criterion 1b. For subjects in group 1 (elderly), hormone replacement therapy, thyroid replacement therapy, prophylactic anti-platelet drugs, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), thiazides, statins, and proton pump inhibitors (PPIs) may be permitted following discussion with the Lilly CRP/CP, or designee.

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

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

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	Urine drug and alcohol screen
Ketones	Hepatitis B surface antigen[a]
Bilirubin	Hepatitis C antibody[a]
Urobilinogen	HIV[a]
Blood	Serum Pregnancy test
Nitrite	FSH[b]
Urine microscopic[c]	Thyroid stimulating hormone[d]

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

[a] Screening only

[b] Screening only for confirmation of post-menopausal status.

[c] Test only if dipstick result is abnormal and per investigator's discretion.

[d] Per investigator's discretion.

Appendix 3 Study Governance, Regulatory and Ethical Considerations

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.