Protocol (c) H8H-MC-LAHU

A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects

NCT03310411

Approval Date: 20-Oct-2017

Protocol H8H-MC-LAHU(c)
A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects

Lasmiditan (LY573144)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 17 August 2017.
Amendment (a) Electronically Signed and Approved by Lilly: 26 September 2017
Amendment (b) Electronically Signed and Approved by Lilly: 10 October 2017
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 20-Oct-2017 GMT

Table of Contents

A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects

Section **Page**

List of Tables

Table **Page**

List of Appendices

1. Protocol Synopsis

Title of Study:
A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects

Rationale:
The study will assess the cardiovascular effects of coadministration of single doses of sumatriptan 100 mg and single doses of lasmiditan 200 mg as measured by vital signs using 24-hour ambulatory blood pressure (ABP) monitoring (ABPM). Pharmacokinetics (PK), safety, and tolerability will also be reported. Sumatriptan is known to cause a transient increase in blood pressure (BP) and is contraindicated in patients with moderate and severe hypertension and mild uncontrolled hypertension. Initial studies with lasmiditan have identified mild effects on cardiovascular parameters (pulse rate [PR] and BP). In clinical practice, lasmiditan may be coadministered with sumatriptan. Therefore, Study H8H-MC-LAHU is being conducted to evaluate the cardiovascular effects and PK impact of coadministration of lasmiditan with sumatriptan in healthy subjects.

Objectives/Endpoints:

Objectives	Endpoints
Primary To compare and contrast the cardiovascular effects of lasmiditan 200 mg and sumatriptan 100 mg administered together to the cardiovascular effects of single doses of either drug administered alone.	Systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and PR per 24-hour ABPM.
Secondary • To evaluate PK of lasmiditan 200 mg and sumatriptan 100 mg administered either alone or together. • To evaluate the safety and tolerability of lasmiditan 200 mg and sumatriptan 100 mg.	• Maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), area under the concentration versus time curve (AUC) from time 0 extrapolated to infinity (AUC)[0-∞]), and AUC from time 0 to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]). • A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

Summary of Study Design:

Study H8H-MC-LAHU is a randomized, double-blind (subject- and investigator-blinded), crossover study with 4 study periods in healthy subjects to investigate the cardiovascular effects, PK, and safety and tolerability of oral

doses of lasmiditan alone, sumatriptan alone, and sumatriptan in combination with lasmiditan. All subjects will participate in 4 treatment periods. The treatments are as follows:

- Treatment A: lasmiditan 200 mg + sumatriptan 100 mg
- Treatment B: lasmiditan 200 mg + placebo
- Treatment C: sumatriptan 100 mg + placebo
- Treatment D: placebo + placebo

Each subject will be randomized to one of 4 treatment sequences in a William's square design (i.e. ABCD, BCDA, CDAB, and DABC).

Treatment Arms and Planned Duration for Individual Subjects:

Screening Period:

All subjects will participate in a screening visit up to 28 days prior to Period 1 study drug dosing.

Treatment Periods:

All subjects will participate in 4 treatment periods. Subjects will be randomized to 1 of 4 treatment sequences. They will be admitted to the clinical research unit (CRU) the day prior to dosing (Day -1) in Period 1, and will be dosed on Day 1 of each treatment period according to their assigned treatment sequence. Subjects will be discharged from the CRU on Day 3 of Period 4, following the collection of all ABP measurements and pharmacokinetic (PK) blood samples. There will be a washout of at least 4 days between each dosing day.

All subjects will be discharged from the study at least 5 days after discharge from Period 4.

Number of Subjects:

Up to 40 subjects may be enrolled to ensure 30 subjects complete the study.

Statistical Analysis:

Cardiovascular parameters that will be assessed by ABPM include peak hourly mean values of SBP, DBP, and MAP, and nadir hourly mean value of PR. The parameters will be listed, and summarized using descriptive statistics, as appropriate. Changes from baseline in cardiovascular parameters SBP, DBP, MAP, and PR will be analyzed to determine the impact of a single dose of sumatriptan 100 mg on the cardiovascular parameters of lasmiditan. A repeated measures linear mixed-effects model with baseline as a covariate, fixed effects for time point, treatment, period (1, 2, 3, or 4), treatment sequence and the treatment by time point interaction, and a random effect for subject will be used. Least squares (LS) means and treatment differences ([lasmiditan + sumatriptan] - [lasmiditan + placebo]) will be calculated and presented with the corresponding confidence intervals (CIs). The same model will be used to assess the impact of a single dose of lasmiditan 200 mg on the cardiovascular parameters of sumatriptan.

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and sumatriptan will be calculated by standard noncompartmental methods of analysis. Pharmacokinetic parameter estimates will be evaluated to determine the impact of a single dose of sumatriptan 100 mg on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated using a linear effects model with fixed effects for treatment, period (1, 2, 3,

or 4), and treatment sequence, and a random effect for subject. From this model, the 90% CIs of the ratios of geometric means from Treatment A (lasmiditan + sumatriptan) will be determined and presented versus those of Treatment B (lasmiditan + placebo). 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. The same model will be independently used to assess the impact of a single dose of lasmiditan 200 mg on the PK of sumatriptan.

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

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHU

	Screening	Periods 1, 2, 3, and 4				Early Discontinuation	Follow-Up	Comments
Procedure	-28 to -2 days prior to Day 1/Period 1	Day -1	Day 1	Day 2	Day 3		At least 5 days after discharge from Period 4	
Informed Consent	X							
Subject Admission to CRU		X						Subject admission will take place in Period 1 only; subjects should remain inpatient until Day 3 of Period 4.
Subject Discharge from CRU					X			Subject discharge from the CRU will take place in Period 4 only.
Randomization			Period 1 only					
Investigational Product Administration			Day 1, indicates Time = 0					Subjects will fast 8 hours before and 3 hours after study drug administration.
Medical History	X	X						After screening, medical history should include interim medical history.
Concomitant Medication	X	X	X	X	X	X	X	
Adverse Event Review	X	X	X	X	X	X	X	
Height	X							
Weight	X							

	Screening	Periods 1, 2, 3, and 4				Early Discontinuation	Follow-up	Comments
Procedure	-28 to -2 days prior to Day 1/Period 1	Day -1	Day 1	Day 2	Day 3		At least 5 days after discharge from Period 4	
Vital Signs (Supine)	X	X	Predose, 1, 2 and 4 h	24 h			X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
ABPM			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.
ABPM Training		X						Subjects should be trained on the ABPM device on the evening of Day -1 in Period 1 only. Data from this acclimation period will not be stored or analyzed.
Orthostatic Vital Signs	X							Time points may be added if warranted and agreed upon between Lilly and the investigator.
Clinical Lab Tests	X	X				X	X	See Appendix 2, Clinical Laboratory Tests, for details.

	Screening	Periods 1, 2, 3, and 4				Early Discontinuation	Follow-up	Comments
Procedure	-28 to -2 days prior to Day 1/Period 1	Day -1	Day 1	Day 2	Day 3		At least 5 days after discharge from Period 4	
Pregnancy Test	X	X				X	X	Serum pregnancy test will be performed at screening. Urine or serum pregnancy test will be performed at admission to Period 1 and at follow-up.
12-Lead ECG	X		Predose	24 h		X		Single ECGs will be taken.
Physical Exam	X	X		X		X	X	Full medical assessment (including neurological examination) will be performed at screening. After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.
Genetic Sample			X					Single sample for pharmacogenetic analysis taken prior to dosing on Day 1 of Period 1.
Lasmiditan and Metabolite PK Samples			Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 and 36 h	48 h			Sampling times are relative to the time of study treatment administration (0 min).
Sumatriptan PK Samples			Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h				Sampling times are relative to the time of study treatment administration (0 min).

	Screening	Periods 1, 2, 3, and 4				Early Discontinuation	Follow-up	Comments
Procedure	-28 to -2 days prior to Day 1/Period 1	Day -1	Day 1	Day 2	Day 3		At least 5 days after discharge from Period 4	
Urine Sample for CrCl			0-6, 6-12, and 12-18 h	18-24, 24-30 and 30-36 h	36-42 and 42-48 h			Urine collection for the determination of CrCl.
Renal Biomarker Samples			Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 and 36 h	48 h			Sampling times are relative to the time of study treatment administration (0 min).

Abbreviations: ABPM = ambulatory blood pressure monitoring; CrCl = creatinine clearance; CRU = clinical research unit; ECG = electrocardiogram; h = hours; 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, vital signs, and 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 supine vital signs measurements are required, repeats should be performed after venipuncture.

3. Introduction

3.1. Study Rationale

Lasmiditan is a small molecule serotonin (5-hydroxytryptamine; 5-HT)$_{1F}$ receptor agonist being developed for the acute treatment of migraine. Triptans, which are 5-HT$_{1B}$ and 5-HT$_{1D}$ 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-HT$_{1B}$ 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-HT$_{1F}$ receptor with >450-fold higher affinity for the 5-HT$_{1F}$ receptor than for 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors (Capi et al. 2017). Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

Sumatriptan is a synthetic triptan used for the treatment of migraine and cluster headaches, known to cause a transient increase in blood pressure (BP), and is contraindicated in patients with moderate and severe hypertension, and mild uncontrolled hypertension.

Sumatriptan has an oral bioavailability of approximately 15%, partially attributable to the presystemic metabolism of sumatriptan via monoamine oxidase (MAO). Due to the predominance of this metabolism pathway, the potential for MAO inhibitors to cause clinically significant drug-drug interactions is high. In vitro studies suggest that lasmiditan is not a monoamine oxidase inhibitor, and it is expected that the likelihood of lasmiditan affecting sumatriptan pharmacokinetics (PK) is low. In clinical practice, lasmiditan may be coadministered with sumatriptan; it is therefore pertinent to determine the potential for pharmacodynamic (PD) or PK drug interactions. This study will assess the effect of single doses of sumatriptan 100 mg on the cardiovascular effects of single doses of lasmiditan 200 mg; the effect of single doses of lasmiditan 200 mg on the cardiovascular parameters of sumatriptan, and the cardiovascular effects of either drug alone, as measured by vital signs using 24-hour ambulatory blood pressure (ABP) monitoring (ABPM). Pharmacokinetics, safety and tolerability will also be reported.

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 (Study COL MIG-201), and up to 400 mg of the oral tablet formulation (COL MIG-202). 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 and 200 mg doses of orally administered lasmiditan achieved superior 2-hour pain free rate and the relief of most bothersome migraine symptoms (nausea, phonophobia, and photophobia) compared to placebo.

Five Phase 1 studies of lasmiditan have been completed and methods of administration included IV, oral, and sublingual. Lasmiditan was tolerated by healthy subjects when administered IV up to 180 mg over 20 or 60 minutes (H8H-BD-LACA; 40 subjects), as a solution formulation 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 of 200 mg (COL MIG-104; 30 subjects) and up to 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; methods of administration included IV, oral, and sublingual. Compared with placebo, the most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) across all studies 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 patient in the Phase 2 dose-ranging study in migraineurs experienced a serious adverse event (SAE) of dizziness that was moderate in severity, occurred approximately 30 minutes after dosing, and was considered related to lasmiditan. The subject was admitted to hospital for overnight observation following review by the hospital emergency room physician.

When administered IV at the highest dose of 180 mg (H8H-MC-LACA), lasmiditan produced a statistically significant but small dose-related decrease in pulse rate (PR) and increase in BP, although the magnitude of these effects was considered unlikely to be of clinical significance in this group of healthy subjects. Following oral administration at doses of up to 400 mg (COL MIG-102), PR again was slightly reduced, but there were no consistent effects on BP. The effects on vital signs were transient, not dose-related, and unlikely to be clinically significant given the intended intermitten7t use of lasmiditan.

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

In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1 to 2.5 hours after a single oral dose ranging from 25 to 400 mg, and the geometric mean terminal half-life was approximately 4 to 6 hours. Lasmiditan exhibited dose-linear PK; low to moderate inter-subject variability in exposure was observed across doses (coefficient of variation [%CV] up to 61% and 45% for maximum observed drug concentration [C_{max}] and area under the curve [AUC], respectively; COL MIG-102). Co-administration of lasmiditan with a high fat diet (COL MIG-104) led to a delay in median time of maximum observed drug concentration (t_{max}) value by approximately 1 hour and a modest (~20%) increase in lasmiditan C_{max} and AUC values, relative to that under fasted conditions.

Following exploratory analysis of human plasma samples from adult subjects receiving oral lasmiditan, 3 major human metabolites (M7, M8, and [S,R]-M18) were observed. Ketoreduction

of lasmiditan to M8 (alcohol) appears to be the major metabolic pathway, presumably via non-CYP enzymes. In human liver microsomes, CYP1A2 and CYP3A4 appear to be involved to a minor extent in lasmiditan metabolism. Unchanged lasmiditan comprises approximately 2% of the dose excreted in urine. Lasmiditan is a very weak inhibitor of CYP3A4, CYP2D6, and P-glycoprotein.

3.3. Benefit/Risk Assessment

The primary objective for this study is to compare and contrast the cardiovascular effects of lasmiditan and sumatriptan, in relation to vital signs following a single oral dose alone or when coadministered in healthy 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. 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).

Sumatriptan is a marketed drug and will be administered within the recommended dose regimen for clinical use (100 mg). Sumatriptan is known to cause transient increases in blood pressure at this dose. This dose regimen has been tolerated in previous PK/PD studies in healthy subjects (for example Nappi et al. 1994). Similar to the adverse events (AEs) observed following dosing with lasmiditan, AEs observed following dosing with sumatriptan include, but are not limited to, fatigue, dizziness, paresthesia, and hot flashes.

Dosing of lasmiditan and sumatriptan in this study will be conducted in an inpatient setting and subjects will be monitored in-house for at least 24 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 investigator's brochure (IB).

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

4. Objectives and Endpoints

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

Table LAHU.1. Objectives and Endpoints

Objectives	Endpoints
Primary To compare and contrast the cardiovascular effects of lasmiditan 200 mg and sumatriptan 100 mg administered together to the cardiovascular effects of single doses of either drug administered alone.	Systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and PR per 24-hour ABPM.
Secondary • To evaluate the PK of lasmiditan 200 mg and sumatriptan 100 mg administered either alone or together. • To evaluate the safety and tolerability of lasmiditan 200 mg and sumatriptan 100 mg.	• C_{max}, t_{max}, area under the concentration versus time curve (AUC) from time 0 extrapolated to infinity (AUC[0-∞]), and AUC from time 0 to time t, where t is the last time point with a measurable concentration (AUC[0-tlast]). • A summary of the number of TEAEs and SAEs.
Exploratory To evaluate the effect of lasmiditan on renal function biomarkers in serum and urine. To evaluate the PK of lasmiditan metabolites alone and in combination with sumatriptan in healthy subjects.	Cystatin C, creatinine, and creatinine clearance C_{max}, t_{max}, AUC(0-tlast) and AUC(0-∞).

5. Study Design

5.1. Overall Design

This is a randomized, double-blind, crossover study with 4 study periods in healthy subjects. All subjects will participate in 4 treatment periods. The treatments are as follows:

- Treatment A: lasmiditan 200 mg + sumatriptan 100 mg
- Treatment B: lasmiditan 200 mg + placebo
- Treatment C: sumatriptan 100 mg + placebo
- Treatment D: placebo + placebo

Each subject will be randomized to one of 4 treatment sequences in a William's square design as outlined in Table LAHU.2.

Table LAHU.2. Sequences in Study LAHU

Sequence	Period 1	Period 2	Period 3	Period 4
1	Lasmiditan + sumatriptan	Lasmiditan + placebo	Sumatriptan + placebo	Placebo + placebo
2	Lasmiditan + placebo	Sumatriptan + placebo	Placebo + placebo	Lasmiditan + sumatriptan
3	Sumatriptan + placebo	Placebo + placebo	Lasmiditan + sumatriptan	Lasmiditan + placebo
4	Placebo + placebo	Lasmiditan + sumatriptan	Lasmiditan + placebo	Sumatriptan + placebo

Screening Period:

All subjects will participate in a screening visit up to 28 days prior to Period 1 study drug dosing.

Treatment Periods:

All subjects will participate in 4 treatment periods. Subjects will be randomized to one of 4 treatment sequences. They will be admitted to the clinical research unit (CRU) the day prior to dosing (Day -1) in Period 1, and will be dosed on Day 1 of each treatment period according to their assigned treatment sequence (Table LAHU.2). Subjects will be discharged from the CRU on Day 3 of Period 4 following the collection of all ABP measurements and PK blood samples. There will be a washout of at least 4 days between each dosing day.

All subjects will be discharged from the study at least 5 days after discharge from Period 4.

5.2. Number of Participants

Up to 40 subjects may be enrolled to ensure 30 subjects complete the study.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

A double-blind (subject- and investigator-blinded), randomized, and placebo-controlled design is being used to minimize bias on the primary objective of this study.

The study blind will be maintained by either use of a blindfold, or placement of the tablets in an amber vial to disguise their appearance; the sumatriptan tablets to be used in this study will be similar in shape and size to both lasmiditan and lasmiditan placebo (round and approximately 10 mm in diameter), therefore lasmiditan placebo will also be used as the placebo for sumatriptan.

A crossover design improves the sensitivity for detecting any cardiovascular signals by means of vital signs (as are described in Section 3.2). Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications.

The washout period is at least 4 days, which is adequate based on the half-life of lasmiditan.

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

Preliminary data suggest that lasmiditan may inhibit renal transporters involved in the active secretion of creatinine into the urine, which can lead to a decrease in the renal clearance of creatinine in vivo and subsequent increase in serum creatinine. The change in creatinine renal clearance is often delayed and transient. Hence, frequent sampling with urine collection is necessary for capturing temporal changes in creatinine disposition. The inclusion of serum cystatin C, which provides a more precise measure of glomerular filtration rate (GFR), enables differentiation between changes in creatinine transport versus change in renal function.

5.5. Justification for Dose

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

The dose of sumatriptan (100 mg) is within the range used in clinical practice. More detailed information can be found in the Sumatriptan Package Insert.

6. Study Population

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

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

Screening may occur up to 28 days prior to enrollment (Day 1). Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

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

[1a] male subjects:

are not required to adhere to contraceptive requirements.

[1b] female subjects:

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

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

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

[3] have a body mass index (BMI) of 19.0 to 35.0 kg/m^2, inclusive, at screening.

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

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

[6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

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

6.2. Exclusion Criteria

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

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

[9] are Lilly or Covance employees.

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

[11] have known allergies to lasmiditan, sumatriptan, related compounds, or any components of the formulations of lasmiditan and sumatriptan.

[12] are persons who have previously received the investigational product in this study, who have been withdrawn from this study, or who have received lasmiditan in any other study investigating lasmiditan within the 3 months prior to screening.

[13] have participated (dosed with any investigational product), within the 30 days prior to Day -1, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[14] have 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.

[15] have a history, signs, or symptoms of arrhythmia or Wolff Parkinson White syndrome that could affect the subject's safety.

[16] have an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 as determined by the CKD-EPI equation:

$GFR = 141 \times \text{minimum}(Scr/\kappa, 1)^{\alpha} \times \text{maximum}(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times$ (1.018 if female) × (1.159 if black).

- Scr is serum creatinine; κ is 0.7 for females and 0.9 for males; α is -0.329 for females and -0.411 for males.

- Minimum indicates the minimum of Scr/κ or 1; maximum indicates the maximum of Scr/or 1.

[17] have a resting SBP >135 mmHg and DBP >85 mmHg at screening. Additional assessments may be performed to confirm eligibility.

[18] have a history of syncope, presyncope, uncontrolled vertigo, postural dizziness, or being at risk for falls, as judged to be clinically significant by the investigator, or have orthostatic decreases in SBP of >20 mmHg, or have orthostatic decreases in DBP of >10 mmHg at screening. May be repeated on 1 occasion if asymptomatic.

[19] have a supine PR of <50 or >90 bpm at screening. Additional assessments may be performed to confirm eligibility.

[20] have significant history of or current cardiovascular, respiratory (including bronchospasm or bronchial asthma, or chronic obstructive airways disease), hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorder, or a condition 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.

[21] have a history, signs, or symptoms of vasospastic coronary artery disease.

[22] a history of allergic reactions to medications or food products.

[23] have known or ongoing neuropsychiatric disorders (for example, manic depressive illness, schizophrenia, depression) considered as clinically significant by the Investigator.

[24] 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.

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

[26] have a history, signs, or symptoms of Raynaud's phenomenon, hypertension, ischemic bowel disease, or peripheral vascular disease.

[27] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65), and 14 units per week (females), or are unwilling to stop alcohol consumption 48 hours prior to admission in Period 1, and whilst resident at the CRU. At all other times, subjects must agree to consume no more than 2 units per day (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

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

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

[30] have received centrally active drugs or those affecting peripheral cholinergic transmission within the 3 months prior to Day -1.

[31] use of monoamine oxidase-A inhibitors and other drugs associated with serotonin syndrome (i.e. selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and 5-HT1 agonists) within the 3 months prior to the first dosing occasion.

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

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

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

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

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

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

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [1] through [7] define a healthy population suitable for evaluation in a Phase 1 study. Criteria [8] and [9] prevent conflict of interest in study participants. Criteria [10] through [38] predominantly exclude medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Lasmiditan and sumatriptan will be administered after an overnight fast of at least 8 hours. On Day 1 of each treatment period, subjects will abstain from water 1 hour before and after dosing (except for water given with the dose). Subjects will remain fasting for approximately 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 in Period 1, and whilst resident at the CRU.

Alcohol – Subjects will not consume alcohol for 48 hours prior to admission in Period 1, and whilst resident at the CRU. At all other times, subjects must consume no more than 2 units per day (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

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

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

6.3.3. Activity

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

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

Investigational products used in this study are shown in Table LAHU.3.

Tablets of lasmiditan and sumatriptan will be administered orally with approximately 240 mL of room temperature water, in a sitting position. Tablets of lasmiditan and sumatriptan will be administered in the morning of Day 1 of each treatment period. Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table LAHU.3. Treatments Administered

Treatment Name	Lasmiditan	Sumatriptan	Placebo (lasmiditan)
Dosage Formulation	film-coated tablet	film-coated tablet	film-coated tablet
Unit Dose Strength/Dosage Level	(1 × 200-mg) tablets/ 200 mg lasmiditan	(1 × 100-mg) tablets/ 100 mg sumatriptan	--
Route of Administration	Oral	Oral	Oral
Dosing Instructions	1 tablet taken in the morning of Day 1	1 tablet taken in the morning of Day 1	1 tablet taken in the morning of Day 1

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study

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

7.1.1. Packaging and Labeling

Each tablet of lasmiditan contains 200 mg of active ingredient and is provided as bulk supplies in bottles. Sumatriptan will be sourced by the investigative site.

Both lasmiditan and sumatriptan tablets are round and 10 mm in diameter. Placebo tablets look similar to both lasmiditan and sumatriptan tablets, but contain no active ingredient. Placebo tablets will be provided in similar bulk bottles as lasmiditan.

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

7.2. Method of Treatment Assignment

All subjects will participate in 4 treatment periods. The treatments are as follows:

- Treatment A: lasmiditan 200 mg + sumatriptan 100 mg
- Treatment B: lasmiditan 200 mg + placebo
- Treatment C: sumatriptan 100 mg + placebo
- Treatment D: placebo + placebo

Each subject will be randomized to one of 4 treatment sequences in a William's square design (i.e., ABCD, BCDA, CDAB, and DABC) using a computer-generated allocation schedule.

7.2.1. Timing of Doses

The doses will be administered at approximately the same time on Day 1 of each treatment period. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

Each subject will either be blindfolded at each dosing occasion, or will receive the study drug in an amber vial, to maintain the study blind. Blinding will also be maintained throughout the conduct of the study as described in the separate Blinding Plan.

Emergency codes will be available to the investigator. A code, which reveals the treatment sequence 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 (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

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

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

Not applicable.

8. Discontinuation Criteria

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

Subjects who do not complete the study will not be replaced.

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 clinical pharmacologist/CRP or designee and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist/CRP or designee to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

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

- the subject requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-Up

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

9. Study Assessments and Procedures

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

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

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

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

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

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

9.2.1. Serious Adverse Events

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

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

Study site personnel must alert the Lilly clinical pharmacologist/CRP, 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 eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to investigational product) does not meet the definition of an 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 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.

Complaints pertaining to lasmiditan in this study will be collected. As sumatriptan will be commercially supplied, Lilly will not collect product complaints on sumatriptan in this study.

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 or sumatriptan is considered any dose higher than the dose assigned through randomization. There is no specific antidote for lasmiditan or sumatriptan. In the event of overdose, the subject should receive appropriate supportive care and AEs should be documented.

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

9.4.2.1. Supine and Orthostatic Vital Signs

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

Blood pressure and 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.

Where orthostatic measurements are required, subjects should be supine for at least 5 minutes and then subjects will stand, and standing blood pressure 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 treatment period if warranted.

9.4.2.2. 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 before the predose measurement in the first treatment period 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 (for example, 0700 hours to 2200 hours) and every 30 minutes throughout the night (2200 hours to 0700 hours). On Day 1 of each treatment period, 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, single 12-lead digital safety ECGs should be collected according to the Schedule of Activities (Section 2). Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

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

Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for at least 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. All ECGs 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 whilst the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subject for symptoms (for example, palpitations, near syncope, syncope) to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

9.4.4. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- AEs

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

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

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevated serum total bilirubin to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an 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 its metabolites, and 3 mL each to determine the plasma concentrations of sumatriptan. 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 and its metabolites will be assayed using a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method.

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

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

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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

9.8.1. Creatinine Clearance

Urine samples (relative to the dosing time of lasmiditan) will be collected according to the Schedule of Activities (Section 2) to determine creatinine clearance. The collection will start at

the time of dosing on Day 1 and will be completed on Day 3 of each treatment period. The actual volume of urine collected and the time of each collection will be recorded.

Creatinine urine samples, together with the serum creatinine measurements, will be used to assess creatinine clearance.

The sample(s) will be stored per institutional standards at a facility selected by the sponsor. During this time, remaining samples may be used for exploratory analyses.

9.8.2. Renal Biomarker Samples

Analysis will be performed on renal function biomarkers, including, but not limited to, creatinine and cystatin C, to evaluate any changes from baseline (predose) following lasmiditan dosing. Venous blood samples will be collected as specified in the Schedule of Activities (Section 2) for determination of serum concentrations of creatinine and cystatin C.

The samples will be identified by subject numbers and stored for a maximum of 2 years after the last subject visit for the 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 40 subjects may be enrolled to ensure 30 subjects complete the study. Assuming standard deviation for the change, within-subject, in SBP of 12.7 mmHg (based on results from study CCI), this will result in a 90% probability that the half-width of the 90% confidence interval (CI) about the mean within-subject change between periods is no larger than 4.6 mmHg.

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 all subjects who have the relevant test and reference treatment measurements.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least one dose of lasmiditan or sumatriptan 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 to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

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

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

10.3.1.2. Statistical Evaluation of Safety

Clinical laboratory and vital signs parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and sumatriptan will be calculated by standard noncompartmental methods of analysis and summarized using descriptive statistics.

The primary parameters for analysis will be C_{max}, t_{max}, AUC(0-tlast), and AUC(0-∞) of lasmiditan, its metabolites, and sumatriptan. 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 the impact of a single dose of sumatriptan 100 mg on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated using a linear effects model with fixed effects for treatment, period (1, 2, 3, or 4) and treatment sequence, and a random effect for subject. From this model, the 90% CIs of the ratios of geometric means from Treatment A (lasmiditan + sumatriptan) will be determined and presented versus those of Treatment B (lasmiditan + placebo).

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.

The same model will be independently used to assess the impact of a single dose of lasmiditan 200 mg on the PK of sumatriptan.

Additional analyses may be performed, as warranted.

10.3.3. Cardiovascular Analyses

10.3.3.1. Cardiovascular Parameter Estimation

The primary parameters for the cardiovascular analyses will be peak hourly mean values of SBP, DBP, and MAP, and nadir hourly mean value of PR, and will be determined by ABPM.

10.3.3.2. Statistical Inference of Cardiovascular Parameters

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

Baseline value will be defined as the mean value during the 2 hours pre-dose for each period. Changes from baseline in cardiovascular parameters SBP, DBP, MAP, and PR will be analyzed to determine the impact of a single dose of sumatriptan 100 mg on the cardiovascular parameters

of lasmiditan. A repeated measures linear mixed-effects model with baseline as a covariate, fixed effects for time point, treatment, period (1, 2, 3, or 4), treatment sequence, and the treatment by time point interaction, and a random effect for subject will be used. Least squares (LS) means and treatment differences ([lasmiditan + sumatriptan] - [lasmiditan + placebo]) will be calculated and presented with the corresponding CIs. The same model will be used to assess the impact of a single dose of lasmiditan 200 mg on the cardiovascular parameters of sumatriptan.

10.3.4. Biomarker Analyses

Exploratory biomarkers such as creatinine clearance, as well as creatinine and cystatin C levels may be listed, and summarized using descriptive statistics.

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

10.3.5. 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

Capi M, de Andrés F, Lionetto L, Gentile G, Cipolla F, Negro A, Borro M, Martelletti P, Curto M. Lasmiditan for the treatment of migraine. *Expert Opin Investig Drugs*. 2017 Feb;26(2):227-234.

Nappi G, Sicuteri F, Byrne M, Roncolato M, Zerbini O. Oral sumatriptan compared with placebo in the acute treatment of migraine. *J Neurol*. 1994;241(3):138-144.

Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve extrapolated from time 0 to infinity
AUC(0-tlast)	area under the concentration versus time curve from time 0 to time t, where t is the last time point with a measurable concentration
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
BP	blood pressure
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.

confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
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
DBP	diastolic blood pressure
ECG	electrocardiogram
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.
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
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug: An application to the Food and Drug Administration to allow testing of a new drug in humans.
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IV	intravenous
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.
MAP	mean arterial pressure
randomize	the process of assigning subjects/patients to an experimental group on a random basis
PK/PD	pharmacokinetic/pharmacodynamic
PR	pulse rate
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.
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
t_{max}	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
Differential WBC absolute counts and % of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase
Eosinophils	Aspartate aminotransferase
Basophils	Alanine aminotransferase
	Creatinine
Urinalysis	Ethanol testing[a]
Specific gravity	Urine drug screen[a]
pH	Hepatitis B surface antigen[b]
Protein	Hepatitis C antibody[b]
Glucose	HIV[b]
Ketones	FSH[c]
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine microscopic (if positive result for blood)	

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

a Urine drug screen and ethanol level will be performed locally at screening and admission to the CRU, and may be repeated at other times indicated in the Schedule of Activities (Section 2).

b Performed at screening only.

c Performed at screening only for confirmation of post-menopausal 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 Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

- the current IB
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

3) applicable laws and regulations

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

Protocol Signatures

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

After reading the protocol, 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 eCRFs, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate eCRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

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

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct 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**
CK	**antibody)[a]**

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatinine kinase; 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-LAHU 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	5	62.5
Serum pregnancy test	5	3	15
Lasmiditan and metabolite pharmacokinetics	2	56	112
Sumatriptan pharmacokinetics	3	45	135
Renal biomarkers	2.5	56	140
Pharmacogenetics	10	1	10
Total			494
Total for clinical purposes (rounded up to the nearest 10 mL)			500

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

Appendix 6. Protocol Amendment H8H-MC-LAHU(c) Summary: A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects

Overview

Protocol H8H-MC-LAHU, A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects, has been amended. The new protocol is indicated by Amendment (c) and will be used to conduct the study in place of any preceding version of the protocol.

Following feedback from the FDA from the Type C meeting on 12 October 2017, the protocol was amended to include an assessment on lasmiditan metabolites. In addition, language was added to clarify the definitions of peak, nadir, and baseline for ABPM.

Revised Protocol Sections

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

1. Protocol Synopsis

Statistical Analysis:

Cardiovascular parameters that will be assessed by ABPM include peak hourly mean values of SBP, DBP, and MAP, and nadir hourly mean value of PR. The parameters will be listed, and summarized using descriptive statistics, as appropriate. Changes from baseline in cardiovascular parameters SBP, DBP, MAP, and PR will be analyzed to determine the impact of a single dose of sumatriptan 100 mg on the cardiovascular parameters of lasmiditan. A repeated measures linear mixed-effects model with baseline as a covariate, fixed effects for time point, treatment, period (1, 2, 3, or 4), treatment sequence and the treatment by time point interaction, and a random effect for subject will be used. Least squares (LS) means and treatment differences ([lasmiditan + sumatriptan] - [lasmiditan + placebo]) will be calculated and presented with the corresponding confidence intervals (CIs). The same model will be used to assess the impact of a single dose of lasmiditan 200 mg on the cardiovascular parameters of sumatriptan.

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and sumatriptan will be calculated by standard noncompartmental methods of analysis. Pharmacokinetic parameter estimates will be evaluated to determine the impact of a single dose of sumatriptan 100 mg on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated using a linear effects model with fixed effects for treatment, period (1, 2, 3, or 4), and treatment sequence, and a random effect for subject. From this model, the 90% CIs of the ratios of geometric means from Treatment A (lasmiditan + sumatriptan) will be determined and presented versus those of Treatment B (lasmiditan + placebo). 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. The same model will be independently used to assess the impact of a single dose of lasmiditan 200 mg on the PK of sumatriptan.

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

Study Schedule Protocol H8H-MC-LAHU

	Screening	Periods 1, 2, 3, and 4				Early Discontinuation	Follow-Up	Comments
Procedure	-28 to -2 days prior to Day 1/Period 1	Day -1	Day 1	Day 2	Day 3		At least 5 days after discharge from Period 4	
Lasmiditan and Metabolite PK Samples			Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 and 36 h	48 h			Sampling times are relative to the time of study treatment administration (0 min).

4. Objectives and Endpoints

Table LAHU.1. Objectives and Endpoints

Exploratory To evaluate the effect of lasmiditan on renal function biomarkers in serum and urine.	Cystatin C, creatinine, and creatinine clearance.
To evaluate the PK of lasmiditan metabolites alone and in combination with sumatriptan in healthy subjects.	C_{max}, t_{max}, AUC(0-tlast) and AUC(0-∞).

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 its metabolites, and 3 mL each to determine the plasma concentrations of sumatriptan. 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 and its metabolites will be assayed using a validated liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) method.

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

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

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and sumatriptan will be calculated by standard noncompartmental methods of analysis and summarized using descriptive statistics.

The primary parameters for analysis will be C_{max}, t_{max}, AUC(0-tlast), and AUC(0-∞) of lasmiditan, its metabolites, and sumatriptan. 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 the impact of a single dose of sumatriptan 100 mg on the PK of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated using a linear effects model with fixed effects for treatment, period (1, 2, 3, or 4) and treatment sequence, and a random effect for subject. From this model, the 90% CIs of the ratios of geometric means from Treatment A (lasmiditan + sumatriptan) will be determined and presented versus those of Treatment B (lasmiditan + placebo).

10.3.3.1. Cardiovascular Parameter Estimation

The primary parameters for the cardiovascular analyses will be peak hourly mean values of SBP, DBP, and MAP, and nadir hourly mean value of PR, and will be determined by ABPM.

10.3.3.2. Statistical Inference of Cardiovascular Parameters

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

Baseline value will be defined as the ~~peak~~ mean value during the 2 hours pre-dose for each period. Changes from baseline in cardiovascular parameters SBP, DBP, MAP, and PR will be analyzed to determine the impact of a single dose of sumatriptan 100 mg on the cardiovascular parameters of lasmiditan. A repeated measures linear mixed-effects model with baseline as a covariate, fixed effects for time point, treatment, period (1, 2, 3, or 4), treatment sequence, and the treatment by time point interaction, and a random effect for subject will be used. Least squares (LS) means and treatment differences ([lasmiditan + sumatriptan] - [lasmiditan + placebo]) will be calculated and presented with the corresponding CIs. The same model will be used to assess the impact of a single dose of lasmiditan 200 mg on the cardiovascular parameters of sumatriptan.

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-LAHU 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	5	62.5
Serum pregnancy test	5	3	15
Lasmiditan and metabolite pharmacokinetics	2	56	112
Sumatriptan pharmacokinetics	3	45	135
Renal biomarkers	2.5	56	140
Pharmacogenetics	10	1	10
Total			494
Total for clinical purposes (rounded up to the nearest 10 mL)			500

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

Leo Document ID = d90b545b-bf55-413e-bff8-e4fb2b5a9925

Approver: PPD
Approval Date & Time: 19-Oct-2017 17:16:34 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 20-Oct-2017 08:36:25 GMT
Signature meaning: Approved