Protocol (a) H8H-MC-LAHC

An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods

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Protocol H8H-MC-LAHC(a)
An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods

Lasmiditan (LY573144)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 08 June 2017.
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1. Protocol Synopsis

Title of Study:
An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods

Rationale:
Lasmiditan is a small molecule 5-HT1F receptor agonist being developed for the acute treatment of migraine. Acute migraine attacks are frequently accompanied by some gastrointestinal symptoms, such as nausea and vomiting. Gastric motility studies also indicated that many migraine patients developed gastroparesis during acute migraine attacks. Changes in gastric motility may lead to changes in pharmacokinetics (PK) of drugs for migraine abortive treatment, which may reduce the effectiveness of migraine treatment. The goal of this study is to assess the PK of lasmiditan in migraineurs during acute migraine attacks and during inter-ictal periods.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
To assess the PK of lasmiditan in patients with episodic migraine during an acute migraine attack and during their inter-ictal period.	For lasmiditan (parent), maximum observed drug concentration (C_{max}), time of C_{max} (t_{max}), area under the concentration versus time curve (AUC) from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), and AUC from zero to infinity (AUC[0-∞]).
Secondary	
To assess the tolerability of a single dose of lasmiditan in patients with episodic migraine.	A summary of the number of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).
To evaluate and compare the PK characteristics of major lasmiditan metabolites (M3, M7, M8, S,R-M18, and S,S-M18) in patients during an acute migraine attack and during the inter-ictal period.	For each metabolite, C_{max}, t_{max}, AUC(0-t_{last}), and AUC(0-∞).

Summary of Study Design:

This is a multi-center, open-label study with 2 study periods to be conducted in patients with episodic migraine. Patients will receive 1 oral dose of lasmiditan during an acute migraine attack (Period 1), and 1 oral dose of lasmiditan during their inter-ictal period (Period 2).

Eligible patients will be instructed to telephone the study site when they feel the onset of migraine symptoms, to arrange to attend for an immediate inpatient stay. Provided they are still experiencing migraine symptoms, patients will receive a single dose of 200 mg lasmiditan on arrival at the study site; this will be defined as Period 1, Day 1.

The first dose of lasmiditan must be administered within 24 hours of onset of migraine symptoms; the time of administration will be defined as time = 0. Patients may be discharged from the study site after the last scheduled Day 2 assessment has been performed (24 hours postdose), at the discretion of the investigator, with subsequent Period 1 assessments performed on an outpatient basis. Patients will then telephone the study site again at the onset of their next migraine attack to arrange for a second inpatient stay, which should be scheduled for as soon as possible after the expected resolution of the migraine attack (ie, the next day or, if the migraine is expected to continue into the next day, the following day). This second visit will be defined as Period 2, Day 1. Provided the patient is still in their inter-ictal period (defined as not currently experiencing migraine symptoms) on arrival at the site, they will be readmitted as an inpatient and receive a single dose of 200 mg lasmiditan. Patients may be discharged from the study site after the last scheduled Day 2 assessment is complete, at the discretion of the investigator, with subsequent Period 2 assessments performed on an outpatient basis.

Treatment Arms and Planned Duration for an Individual Patient:
All patients will receive 1 oral dose of lasmiditan during an acute migraine attack (Period 1), and 1 oral dose of lasmiditan during their inter-ictal period (Period 2).

All patients will participate in a screening visit. Each patient must be admitted to the study site with continuing migraine symptoms within 28 days of the screening visit for Period 1 lasmiditan dosing. Period 2 dosing should occur at least 1 week, and up to 4 weeks (but may be extended beyond 4 weeks if necessary, at the investigator's discretion) after the first lasmiditan dose. All patients will return for a follow-up visit 4 to 7 days after their last dose of lasmiditan.

Number of Patients:
Approximately 20 patients may be enrolled so that at least 12 patients with adequate PK data complete the study.

Statistical Analysis:

Pharmacokinetic parameter estimates will be evaluated to determine the impact of changes in gastric motility that may accompany acute migraine attacks on the PK of lasmiditan and its metabolites. Log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) parameters will be evaluated in a linear mixed-effects model with a fixed effect for period (ie, migraine status; lasmiditan administered during a migraine versus lasmiditan administered during the inter-ictal period) and a random effect for patient. The treatment differences will be back transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

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

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHC

	Screening	Periods 1 and 2				Follow-up/ED (4-7 days after last dose)	Comments
Procedure	≤28 days prior to Day 1, Period 1	Day 1	Day 2	Day 3	Day 4		
Informed Consent	X						
Patient Admission to Study Site		X					Period 1 admission at onset of migraine symptoms.
Patient Discharge from Study Site			X				Discharge on Day 2 after last assessment, at investigator discretion.
Investigational Product Administration		X, indicates time = 0					Period 1 dose to be administered within 24 h of onset of migraine symptoms; Period 2 dose to be administered at approximately the same time of day as the Period 1 dose, following a washout of at least 1 week.
Medical History	X						
Medication Review	X	X	X	X	X	X	
Height	X						
Weight	X					X	
Adverse Event Recording		X	X	X	X	X	
Vital Signs (supine)	X	Predose, 1, 2, 4, and 8 h	24 h	48 h	72 h	X	Supine triplicate BP and pulse rate, except screening. Predose vital signs can be taken any time prior to dosing on Day 1. Time points may be added if warranted and agreed upon between Lilly and the investigator. Sampling windows: 1-2 h ±5 min; 4 h ±10 min; 8 h ±20 min; 24-72 h ±30 min.
Orthostatic Vital Signs	X	Predose, 1, 2, 4, and 8 h	24 h			X	Single orthostatic BP/pulse rate. Last triplicate vital sign can be used as the supine vital sign for calculation of orthostatic changes. Time points may be added if warranted and agreed upon between Lilly and the investigator.

	Screening	Periods 1 and 2				Follow-up/ED (4-7 days after last dose)	Comments
Procedure	≤28 days prior to Day 1, Period 1	Day 1	Day 2	Day 3	Day 4		
Clinical Lab Tests	X	Predose	X			X	See Appendix 2, Clinical Laboratory Tests, for details.
Pregnancy Test	X	Predose				X	Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at every admission period prior to dose and at follow-up/ED, if applicable.
Physical Exam /Medical Assessment	X	Predose	X		X	X	Full physical exam at screening; symptom-driven medical assessment at all other times as deemed necessary by the investigator.
12-Lead ECG	X	Predose	24 h			X	Single ECGs to be collected at each time point.
C-SSRS and Self-Harm Supplement	X	X	X			X	At screening 'Baseline' questionnaire to be used, all other timepoints use 'Since Last Visit' questionnaire.
PK Samples		Predose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 18 h	24 h	48 h	72 h		Sampling windows: 0.5-2.5 h ±5 min; 3-6 h ±10 min; 8-12 h ±20 min; 18-72 h ±30 min.
Pharmacogenetic Sample		X					Single sample for pharmacogenetic analysis taken at any time after admission but prior to dosing on Day 1 of Period 1 only.
Exploratory Biomarkers		Predose, 1, 2, and 8 h					

Abbreviations: BP = blood pressure; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; h = hour; 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.

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.

Acute migraine attacks are frequently accompanied by some gastrointestinal symptoms, such as nausea and vomiting. Gastric motility studies also indicated that many migraine patients developed gastroparesis during acute migraine attacks. Changes in gastric motility may lead to changes in the pharmacokinetics (PK) of drugs for migraine abortive treatment, which may reduce the effectiveness of migraine treatment. The goal of this study is to assess the PK of lasmiditan in migraineurs during acute migraine attacks and during inter-ictal periods.

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 (SAMURAI), where 1856 patients were randomized to 100 mg lasmiditan (630 patients), 200 mg lasmiditan (609 patients), or placebo (617 patients). In the SAMURAI study, both 100 and 200 mg doses of orally administered lasmiditan achieved superior 2-hour pain-free rate and relief of the most bothersome migraine symptoms (from the associated symptoms of nausea, phonophobia, and photophobia) compared to placebo.

Five Phase 1 studies of lasmiditan have been completed and methods of administration included IV, sublingual, and oral. Single doses of lasmiditan were tolerated by healthy subjects when administered IV up to 180 mg over 60 minutes (40 subjects), as solution formulations administered orally or sublingually up to doses of 400 and 32 mg, respectively (60 subjects), and as oral tablets up to doses of 200 mg (30 subjects) or 400 mg (44 subjects and 55 subjects).

Across the completed Phase 1, 2, and 3 clinical studies, doses of 0.1 to 400 mg of lasmiditan were evaluated in healthy subjects or migraineurs. To date, lasmiditan has been administered to 213 healthy subjects, and to 1632 migraineurs. 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. Compared with placebo, the most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) included dizziness (very common; more than 1 in 10 patients), somnolence,

fatigue, and paresthesia (common; more than 1 in 100 patients); consistent with the TEAEs seen in other clinical studies of lasmiditan. Hot flashes have also been reported with lasmiditan. The majority of the TEAEs observed in this study were mild or moderate in severity and none led to patient 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 of lasmiditan 200 mg, and was considered probably related to lasmiditan. The subject was admitted to hospital for overnight observation following review by the hospital emergency room physician.

In one study, when administered intravenously up to the highest dose of 180 mg, 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. The decreases in mean heart rate and increases in blood pressure occurred during a short period of time, near the end of the infusions (20 and 60 minutes), corresponding to the timeframe of lasmiditan bioavailability in plasma. Following oral administration at doses of up to 400 mg in another study, 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. The effects of lasmiditan on diastolic and systolic blood pressure and heart rate were evaluated with a PK-pharmacodynamic modeling approach in 2 studies in migraineurs and healthy subjects, respectively. The magnitudes of the identified effects of lasmiditan at the highest plasma concentration levels on vital signs were all within the observed range of random fluctuations in these measurements.

Oral tablet doses of lasmiditan up to 400 mg did not result in any clinically relevant changes in electrocardiograms (ECGs) (including QT/corrected QT [QTc] duration) following administration to healthy subjects. In the thorough QT study in healthy subjects, no clinically significant changes in blood pressure, heart rate, or 12-lead ECG were observed following single oral doses of 100 or 400 mg. 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 following single oral doses ranging from 25 to 400 mg, and the geometric mean terminal half-life was approximately 4 to 6 hours. Lasmiditan exhibited dose-linear PK; low to moderate inter-subject variability in exposure was observed across doses (coefficient of variation [CV%] up to 61% and 45% for maximum observed drug concentration [C_{max}] and area under the curve [AUC], respectively). Renal clearance of lasmiditan was low, with approximately 2% of unchanged lasmiditan recovered by 24 hours postdose. Co-administration of lasmiditan with a high fat diet led to a delay in median time of maximum observed drug concentration (t_{max}) of 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.

Human metabolism has been investigated using liquid chromatography-tandem mass spectrometry (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). The major route of lasmiditan metabolism in humans is likely through non-cytochrome P450 (CYP)-mediated ketone reduction, though minor CYP-mediated metabolism via CYP1A2 and CYP3A4 was noted in vitro. The relative proportions of metabolites to parent drug remained reasonably constant throughout the oral dose range studied and their PK were approximately linear. The half-life of the metabolites ranged from ~4.5 hours to >12 hours.

3.3. Benefit/Risk Assessment

Patients with episodic migraine will receive lasmiditan as a single oral dose of 200 mg during an acute migraine attack and during their inter-ictal period. In the SAMURAI study, both 100- and 200-mg doses of orally administered lasmiditan achieved superior 2-hour pain-free rate and relief of the most bothersome migraine symptoms (from the associated symptoms of nausea, phonophobia, and photophobia) compared to placebo; therefore, patients may experience relief of their migraine symptoms when receiving lasmiditan during the acute migraine attack. Administration of lasmiditan during the inter-ictal period is not anticipated to offer any benefit to the patient.

Lasmiditan has been tolerated by healthy subjects as single oral doses up to 400 mg and by migraineurs as single oral doses up to 200 mg. No clinically significant safety or tolerability concerns have been identified in subjects to date for lasmiditan up to the highest single oral dose given (400 mg). Dosing of lasmiditan in this study will be conducted in an inpatient setting, and patients 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 adverse events (AEs) of lasmiditan are to be found in the Investigator's Brochure (IB).

4. Objectives and Endpoints

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

Table LAHC.1. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the PK of lasmiditan in patients with episodic migraine during an acute migraine attack and during their inter-ictal period.	For lasmiditan (parent) C_{max}, t_{max}, AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), and AUC from zero to infinity (AUC[0-∞]).
Secondary To assess the tolerability of a single dose of lasmiditan in patients with episodic migraine. To evaluate and compare the PK characteristics of major lasmiditan metabolites (M3, M7, M8, S,R-M18, and S,S-M18) in patients during an acute migraine attack and during the inter-ictal period.	A summary of the number of TEAEs and SAEs. For each metabolite, C_{max}, t_{max}, AUC(0-t_{last}), and AUC(0-∞).
Exploratory To assess the effect of lasmiditan on exploratory biomarkers.	Blood levels of CCI [redacted] and/or other biomarkers of interest.

5. Study Design

5.1. Overall Design

Study H8H-MC-LAHC is a multi-center, open-label study with 2 study periods to be conducted in patients with episodic migraine. Patients will receive 1 oral dose of lasmiditan during an acute migraine attack (Period 1), and 1 oral dose of lasmiditan during their inter-ictal period (Period 2). There will be a washout period of at least 1 week between doses.

All patients will participate in a screening visit. Eligible patients will be instructed to telephone the study site when they feel the onset of migraine symptoms, to arrange to attend for an immediate inpatient stay. Each patient must be admitted to the study site with continuing migraine symptoms within 28 days of the screening visit. Provided they are still experiencing migraine symptoms, patients will receive a single dose of 200 mg lasmiditan on arrival at the study site; this will be defined as Period 1, Day 1. The first dose of lasmiditan must be administered within 24 hours of onset of migraine symptoms; the time of administration will be defined as time = 0. Patients may be discharged from the study site after the last scheduled Day 2 assessment has been performed (24 hours postdose), at the discretion of the investigator, with subsequent Period 1 assessments performed on an outpatient basis. Patients will then telephone the study site again at the onset of their next migraine attack to arrange for a second inpatient stay, which should be scheduled for as soon as possible after the expected resolution of the migraine attack (ie, the next day or, if the migraine is expected to continue into the next day, the following day). This second visit should occur at least 1 week, and up to 4 weeks (but may be extended beyond 4 weeks if necessary, at the investigator's discretion) after their first lasmiditan dose, and will be defined as Period 2, Day 1. Provided the patient is still in their inter-ictal period (defined as not currently experiencing migraine symptoms) on arrival at the site, they will be readmitted as an inpatient and receive a single dose of 200 mg lasmiditan. Patients may be discharged from the study site after the last scheduled Day 2 assessment is complete, at the discretion of the investigator with subsequent Period 2 assessments performed on an outpatient basis. All patients will return for a follow-up visit 4 to 7 days after their last dose of lasmiditan.

Blood samples will be collected predose and up to 72 hours postdose in each period for the measurement of plasma concentrations of lasmiditan and its 5 major metabolites.

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

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Approximately 20 patients may be enrolled so that at least 12 patients with adequate PK data complete the study. For the purposes of this study, a patient completes the study when all PK sampling procedures shown in the Schedule of Activities have been finished.

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 patient.

5.4. Scientific Rationale for Study Design

The aim of the study is to assess the PK of a single dose of lasmiditan during an acute migraine attack and during the inter-ictal period. The study has an open-label design in which each patient with episodic migraine will receive a single dose of lasmiditan during a migraine attack and during their inter-ictal period, allowing each patient to act as his/her own control for PK comparisons. The dose of lasmiditan administered during a migraine attack will be assigned to Period 1 for all patients to reduce drop-out rates; Period 2 will be conducted only when PK sampling has been completed during a migraine attack. A single dose of lasmiditan was selected to represent the expected usage of lasmiditan in clinical practice. The washout period between lasmiditan doses of at least 1 week is considered sufficient based on the half-life of lasmiditan of approximately 4 to 6 hours. Vital signs will be measured in triplicate at regular intervals because increases in blood pressure and decreases in heart rate were observed with lasmiditan in a previous study, although these were not considered clinically significant.

5.5. Justification for Dose

Single oral doses of up to 400 mg lasmiditan were tolerated by healthy subjects and single oral doses of up to 200 mg were tolerated by migraineurs in previous studies. The dose level in the current study is 200 mg, which is in the therapeutic dose range and is expected to be the highest potential recommended single dose for lasmiditan.

6. Study Population

Eligibility of patients 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 of Period 1). Patients 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

Patients are eligible for inclusion in the study only if they meet all of the following criteria at screening and enrollment (Day 1 of Period 1):

[1] males or females with history of migraine with or without aura, as defined by International Headache Society (IHS) International Classification of Headache Disorders (ICHD)-3 beta guidelines (1.1 and 1.2) (ICHD-3 beta, Cephalalgia 2013), for at least 1 year, based on medical history. Patients must have experienced 4 to 8 moderate to severe migraines per month that require medication (not including prophylactic migraine prevention treatments) during the 3 months prior to screening, based on medical history. The migraines that require medical treatment must be accompanied by at least 1 of the following associated symptoms: photophobia, phonophobia, nausea, or aura. Patients with other types of headaches in addition to migraine (for example, cluster headache, Medication Overuse Headache, tension type headache) will be allowed to enroll as long as the patient can reliably differentiate migraine and non-migraine headaches AND the patient has had fewer than 5 non-migraine headaches per month during the 3 months prior to screening, based on medical history.

[1a] female patients:

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 dose of lasmiditan. Reliable methods of contraception for female patients 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-childbearing potential, ie, 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 patient is taking hormone replacement therapy (HRT).

[2] are in good health other than migraine, based on medical history, physical examination, clinical laboratory tests, and 12-lead ECG.

[3] are at least 18 years old at the time of screening.

[4] have a body mass index (BMI) of 18.0 to 40.0 kg/m^2, inclusive, at screening.

[5] have clinical laboratory test results at screening 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.

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

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

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

6.2. Exclusion Criteria

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

[9] 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.

[10] are Lilly or Covance employees.

[11] 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.

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

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

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

[15] have an abnormal blood pressure, defined as systolic blood pressure ≤90 or >155 mmHg or diastolic blood pressure ≤50 or >95 mmHg (applies at screening only). Up to 2 additional measurements may be undertaken after an appropriate resting interval at screening to confirm eligibility.

[16] have clinically significant ECG findings, including a QT interval corrected for heart rate using Fridericia's formula (QTcF) value >450 ms (males) or >470 ms (females), clinically significant bradycardia, cardiac block, or bradyarrhythmias.

[17] have a history of, show evidence of, or are undergoing treatment for significant active neuropsychiatric disease (for example, manic depressive illness, schizophrenia, major depressive disorder).

[18] 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) within the past 6 months;
- central nervous system infection or transient ischemic attack (TIA); stroke with persistent neurological deficit (focal or diffuse). 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;
- 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).

[19] have a history of gastrointestinal surgery, or a history of or current irritable bowel syndrome, mal-absorptive disorders, or other gastrointestinal motility disorders. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable.

[20] have current hypertension, unless adequately controlled by a medication that is permitted per the study protocol, in the opinion of the investigator.

[21] have significant history of, or currently have, any other cardiovascular, respiratory (including bronchospasm or bronchial asthma, or chronic obstructive airways disease), hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data, in the opinion of the investigator.

[22] show evidence of substance use disorder as defined in Diagnostic and Statistical Manual of Mental Disorders (DSM) 5, or have positive findings on the drugs of abuse test at the screening visit.

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

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

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

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

[27] have used or intend to use any migraine prevention treatments (including, but not limited to, propranolol or topiramate) within 30 days prior to dosing and until the follow-up visit.

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

[29] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (females and males over 65), or are unwilling to follow the study site's alcohol consumption restrictions while resident (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).

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

[31] have a recent history of a suicide attempt (30 days within screening visit and any time between screening visit and baseline); or are clinically judged by the investigator to be at risk for suicide.

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [1] through [8] define a population with episodic migraine that is suitable for evaluation in a Phase 1 study. Criteria [9] and [10] prevent conflict of interest in study participants. Criteria [11] through [31] 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, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Lasmiditan should be administered after a 4-hour fast, as far as is reasonably practicable, and food should not be consumed until 4 hours postdose. The actual timing of meals on dosing days will be captured in the electronic case report form (eCRF). Water may be consumed ad libitum at all times.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine – Patients will abide by study site restrictions for consumption of xanthine- or caffeine-containing food and drinks while resident.

Alcohol – Patients will abide by study site alcohol consumption restrictions while resident.

Tobacco – Patients will refrain from smoking from 1 hour prior to dosing until 4 hours postdose, and will abide by any study site smoking restrictions while resident.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. The interval between re-screenings should be at least 1 week. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

Lasmiditan will be supplied as film-coated tablets each containing 100 mg or 200 mg of lasmiditan as free base.

One 200-mg tablet or two 100-mg tablets of lasmiditan will be administered orally with approximately 240 mL of room temperature water on each dosing day, in a sitting position. In the event of migraine symptoms, patients may be permitted to receive lasmiditan in a semi-recumbent position, at the discretion of the investigator. Patients will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

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.

7.1.1. Packaging and Labeling

Each tablet of lasmiditan contains 100 mg or 200 mg of active ingredient and is provided as bulk supplies in bottles.

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

7.2. Method of Treatment Assignment

All patients will receive the same treatments in the same sequence and will not be subject to randomization.

7.2.1. Selection and Timing of Doses

The dose administered during a migraine attack must be administered within 24 hours of the onset of migraine symptoms. For each patient, the doses will be administered at approximately the same times on each day, although the dosing times will vary between patients. The actual time of all dose administrations will be recorded in the patient's eCRF.

7.3. Blinding

This is an open-label study.

7.4. Dose Modification

Dose modification will not be allowed during the study. Should a patient fail to tolerate the first dose of lasmiditan, they may be withdrawn from the study at the discretion of the investigator.

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

The use of medications for stable medical conditions that are not excluded per the protocol inclusion/exclusion criteria is allowed, at the investigator's discretion, and following approval by the clinical pharmacologist/clinical research physician (CRP), or designee. Those medications that impact gastric motility should be avoided. The use of medications and/or procedures for acute treatment of migraine or other pain or injury is allowed, with some limitations. The migraine attack that defines Period 1, Day 1 should not be treated with any medication, including, but not limited to, triptans, ergotamines, or analgesic medications. All other migraine attacks occurring during the study may be treated according to the following limitations: triptans and ergotamines should be used within labeled recommendations (and not to exceed 9 days per month in total); acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs are allowed on headache days and for minor ailments (not to exceed 14 days per month in total). Triptans, ergotamines, and analgesics should be avoided for 24 hours prior to dosing in Period 2. Any medications or procedures to prevent migraine (including, but not limited to, propranolol and topiramate) are not allowed within 30 days prior to the first dose and until the follow-up visit.

Patients will be instructed to consult with the investigator or study coordinator at the site before taking any new prescribed medications, over-the-counter medications, or supplements. If the need for other concomitant medication arises, inclusion or continuation of the patient 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

Lasmiditan will not be made available to patients after the end of the study.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

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

- ALT (alanine aminotransferase) or AST (aspartate aminotransferase) > 8× upper limit of normal (ULN)
- ALT or AST >5× ULN sustained for more than 2 weeks or
- ALT or AST >3× ULN and total bilirubin level >2× ULN or International Normalized Ratio (INR) >1.5 or
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP (alkaline phosphatase) >3× ULN
- ALP >2.5× ULN and total bilirubin >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient 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

Patients 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 patient should be discontinued from the study

  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent

- Patient Decision
  - the patient, or legal representative, requests to be withdrawn from the study.

8.3. Patients Lost to Follow-Up

A patient 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 patients 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 patients 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 patient.

The investigator is responsible for the appropriate medical care of patients 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 patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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

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

A "reasonable possibility" means that there is a potential cause and effect relationship between the 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/clinical pharmacologist, or its designee, of any SAE as soon as practically possible.

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

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

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

Pregnancy (maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

For the purposes of this study, an overdose of lasmiditan is considered any dose higher than the planned study dose. There is no specific antidote for lasmiditan. In the event of overdose, the patient 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 patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

9.4.2. Vital Signs

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

Blood pressure and pulse rate should be measured after at least 5 minutes supine. All supine blood pressure and pulse rate measurements except for screening will be done in triplicate at approximately 1-minute intervals. The last triplicate vital sign can be used as the supine vital sign for the calculation of orthostatic changes.

Where orthostatic measurements are required, patients should be supine for at least 5 minutes and stand for at least 2 minutes.

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

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

9.4.3. Electrocardiograms

For each patient, ECGs should be collected according to the Schedule of Activities (Section 2) and the study-specific recommendations included in the Manual of Operations for the study.

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

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities. Electrocardiograms must be recorded before collecting any blood samples. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient 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 patient can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Colombia Suicide Severity Rating Scale

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

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

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

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

self-injurious behavior. Of course, if this situation arises, it is recommended that the patient be referred to a psychiatrist or appropriately trained professional.

The Lilly Self-Harm Supplement should be completed every time the C-SSRS is administered. If there are positive findings on the Self-Harm Supplement, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

9.4.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- AEs

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

9.4.5.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated total bilirubin ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, total bilirubin level, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine 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 2 or more consecutive blood tests
- elevated serum total bilirubin level 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
- patient 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 5 major metabolites. A maximum of 3 samples may be collected at additional time points during each study period 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 5 major metabolites will be measured 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 or the probe substrates.

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

9.6. Pharmacodynamics

This section is not applicable for this study.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, 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 patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient 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

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

Blood samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2), where local regulations allow. Biomarkers assayed may include CCI and CCI, as well as additional biomarkers that may be of interest in future diagnostics/treatments of neurological conditions.

Samples will be used for research on the drug target, disease process, variable response to lasmiditan, pathways associated with migraine, mechanism of action of lasmiditan, and/or research method, or for validating diagnostic tools or assay(s) related to migraine.

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

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, 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.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 20 patients may be enrolled to ensure 12 patients with adequate PK data complete the study. Patients who do not complete both periods of the study may be replaced.

For AUC or C_{max}, assuming inter-patient CV% of 40% (based on previous studies) and a sample size of 12, the 90% confidence interval around the geometric mean of the within-patient ratios (migraine/inter-ictal) will have a half-width of 20.1% with 90% coverage probability.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of patient disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The patients' age, sex, weight, height, BMI, race, and other demographic characteristics, along with baseline disease 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 patients who receive at least one dose of the investigational product and have evaluable PK.

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

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

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

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

10.3.1.2. Statistical Evaluation of Safety

Safety laboratory parameters and vital signs 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 and its metabolites will be calculated by standard noncompartmental methods of analysis and will be listed and summarized for each period using descriptive statistics.

The primary parameters for analysis will be C_{max}, AUC(0-t_{last}), AUC(0-∞), and t_{max} of lasmiditan and its 5 major metabolites (M3, M7, M8, S,R-M18, and S,S-M18). 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 changes in gastric motility that may accompany acute migraine attacks on the PK of lasmiditan and its metabolites. Log-transformed C_{max}, AUC(0-t_{last}), and AUC(0-∞) parameters will be evaluated in a linear mixed-effects model with a fixed effect for period (ie, migraine status; lasmiditan administered during a migraine versus lasmiditan administered during the inter-ictal period) and a random effect for patient. The treatment differences will be back transformed to present the ratios of geometric means and the corresponding 90% confidence interval.

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

Additional analysis may 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

Posner K, Oquendo MA, Gould M, Stanley B, Davies M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. *Am J Psychiatry*. 2007;164(7):1035-1043.

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient 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-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
BMI	body mass index
CCI	CCI
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.
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	coefficient of variation
CYP	cytochrome P450
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	electrocardiogram

eCRF	electronic case report form
EEG	electroencephalogram
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD	International Classification of Headache Disorders
IHS	International Headache Society
informed consent	A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	International Normalized Ratio
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
LC-MS/MS	liquid chromatography-tandem mass spectrometry

Legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient'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 patients 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.
CCI	CCI
PK	pharmacokinetic(s)
QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
randomize	the process of assigning 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
TIA	transient ischemic attack
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 (fasting)
Platelets	Blood urea nitrogen (BUN)
Differential WBC absolute counts and % of:	Total protein
Neutrophils	Albumin
Lymphocytes	Total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
	Creatinine
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	Ethanol testing[a,b]
Ketones	Urine drug screen[a,b]
Bilirubin	Hepatitis B surface antigen[a]
Urobilinogen	Hepatitis C antibody[a]
Blood	HIV[a]
Nitrite	Pregnancy test (females)[c]
Urine microscopic (if positive result for blood)	FSH (females, if applicable)[a,d]

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

[a] Performed at screening only.

[b] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit.

[c] Female patients only. Serum pregnancy test will be performed at screening; urine pregnancy test will be performed at all other time points, and at the investigator's discretion.

[d] Postmenopausal women only.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient 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 patient 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 patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient'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.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

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

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

Regulatory Considerations

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

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

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

Protocol Signatures

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

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 final report coordinating investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

One investigator will be chosen to serve as the final report coordinating investigator.

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 patient 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 patient personal information collected will be provided in a written document to the patient by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	18	1	18
Clinical laboratory tests[a]	8	6	48
Pharmacokinetics[b]	2	38	76
Blood discard for cannula patency	1	38	38
Pharmacogenetics	10	1	10
Exploratory biomarkers	8.5	8	68
Total			258
Total for clinical purposes [rounded up to nearest 10 mL]			260

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

[b] Includes a possible additional 3 samples per study period.

Appendix 6. Protocol Amendment H8H-MC-LAHC(a) Summary: An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods

Protocol H8H-MC-LAHC, An Open-Label, Two-Period Study to Evaluate the Pharmacokinetics of Lasmiditan in Migraineurs During Acute Migraine Attacks and During Inter-Ictal Periods, has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- For consistency with another study in the lasmiditan clinical program and to better tie in with the C-SSRS questionnaire, an exclusion criterion [#31] has been added to rule out suicidal ideation within the past 30 days.
- The wording of Exclusion criterion [#17] has also been adapted for consistency with the other study.
- The stipulation that ECG parameters will be listed has been removed, as this will not be the case. Clinically significant ECG findings will be captured as AEs.

Revised Protocol Sections

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

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

6.2. Exclusion Criteria

[17] have a history of, show evidence of, or are undergoing treatment for significant active neuropsychiatric disease (for example, manic depressive illness, schizophrenia, major depressive disorder).

[31] have a recent history of a suicide attempt (30 days within screening visit and any time between screening visit and baseline); or are clinically judged by the investigator to be at risk for suicide.

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [1] through [8] define a population with episodic migraine that is suitable for evaluation in a Phase 1 study. Criteria [9] and [10] prevent conflict of interest in study participants. Criteria [11] through [3~~0~~1] exclude medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints.

10.3.1.2. Statistical Evaluation of Safety

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

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