Protocol H8H-MC-LAHT(c)

Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

NCT03308669

Approval Date: 20-Oct-2017

Protocol H8H-MC-LAHT(c)
Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

Confidential Information

Lasmiditan (LY573144)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly: 03 August 2017
Amendment (a) Electronically Signed and Approved by Lilly: 05 September 2017
Amendment (b) Electronically Signed and Approved by Lilly: 11 October 2017
Amendment (c) Electronically Signed and Approved by Lilly on approval date provided below.

Approval Date: 20-Oct-2017 GMT

Table of Contents

Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

1. Protocol Synopsis

Title of Study:
Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

Rationale:
Topiramate is indicated for prophylaxis of migraine and may be used concomitantly with lasmiditan in the intended patient population. Study H8H-MC-LAHT (LAHT) is being conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of lasmiditan when co-administered with topiramate in healthy subjects.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of a single dose of lasmiditan in combination with topiramate in healthy subjects.	A summary of the number of treatment-emergent adverse events and serious adverse events.
Secondary	
To evaluate the PK of lasmiditan alone and in combination with topiramate in healthy subjects.	Maximum observed drug concentration (C_{max}), time of C_{max} (t_{max}), area under the concentration versus time curve from zero to last, and zero to infinity
To evaluate the PK of topiramate alone and in combination with lasmiditan.	C_{max}, t_{max}, and area under the concentration versus time curve during 1 dosing interval

Summary of Study Design:

Study LAHT is a parallel, placebo-controlled, fixed-sequence study that assesses the safety, tolerability, and potential for PK interaction between investigator- and subject-blind lasmiditan/placebo and open-label topiramate.

A single dose of lasmiditan (200 mg) or placebo will be administered on the morning of Day 1. Topiramate 25 mg once daily (Day 3), 25 mg twice daily (BID) (Days 4 to 7), 50 mg BID (Days 8 to 13), followed by a single 50-mg dose on the morning of Day 14 will be administered. A single dose of lasmiditan (200 mg) or placebo will be co-administered with topiramate (50 mg) on the morning of Day 14.

Treatment Arms and Planned Duration for Subjects:

Screening Period: All subjects will participate in a screening visit of up to 28 days.
Treatment period: The subjects will be admitted to the clinical research unit (CRU) on the day before dosing (Day -1). Subjects will be discharged from CRU on Day 16 when all study procedures have been completed.
Follow-up period: Subjects will be discharged from the study approximately 10 days after the last dose of topiramate.

Number of subjects:
Approximately 30 subjects may be enrolled so that at least 21 complete the study.

Statistical Analysis:

Safety parameters that will be assessed include safety laboratory parameters, vital signs, neurological examination, Columbia Suicide Severity Rating Scale, and 12-lead electrocardiogram parameters. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and topiramate will be calculated using standard noncompartmental methods of analysis. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameters will be evaluated to determine the impact of topiramate co-administration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and area under the concentration versus time curve parameters will be evaluated in a linear mixed-effects model with fixed effects for treatment (lasmiditan co-administered with topiramate [Day 14; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

A similar analysis will be performed to determine the impact of co-administration of a single dose of lasmiditan on the steady-state PK of topiramate. The model will include the following treatments: topiramate co-administered with lasmiditan (Day 14; test treatment) versus topiramate alone (Day 13; reference treatment).

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

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHT

	Screening		Study Days														Discharge	Follow-up/ED	Comments
Procedure	**-28 to -2 days prior to Day 1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Day 16**	**~10 days after last dose**	
Informed Consent	X																			
Subject Admission to CRU		X																		
Subject Discharge from CRU																		X		
Lasmiditan/Placebo Administration			X Day 1, indicates Time = 0													X				
Topiramate Administration					X	X	X	X	X	X	X	X	X	X	X	X				25 mg QD on Day 3, 25 mg BID from Day 4 to 7, 50 mg BID from Day 8 to 13, a single 50-mg dose on the morning of Day 14
Neurological Examination		X	X		X	X				X					X	X		X		On dosing days, all time points predose and 4-hour postdose for morning dose only. Day 3 is predose only. Non-

	Screening		Study Days														Discharge	Follow-up/ED	Comments
Procedure	**-28 to -2 days prior to Day 1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Day 16**	**~10 days after last dose**	
																				dosing days at single time point.
C-SSRS/Self-Harm	X	X																X	X	
Medical History	X																			
Height	X																			
Weight	X	X																X		Body weight should be recorded on Day -1 of all study periods.
Vital Signs (supine)	X	X	0, 2, 4, 8 h	24 h	0 & 2 h	0 & 2 h				0 & 2 h					0, 2, 4, 8 h	0, 2, 4, 8 h	24 h	X	X	On dosing days, time points correspond to morning dose only. Day 3 time points at evening dose. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.

	Screening		Study Days														Discharge	Follow-up/ED	Comments
Procedure	**-28 to -2 days prior to Day 1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Day 16**	**~10 days after last dose**	
																				Triplicate BP monitoring
Orthostatic Blood Pressure	X		0, 2, & 4 h												0, 2, & 4 h	0, 2, & 4 h				Day 13 time points at morning dose only.
Clinical Laboratory Tests	X	X							X						X			X		See Appendix 2, Clinical Laboratory Tests, for details.
Pregnancy Test	X	X																X		Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at every admission period and at poststudy, if applicable.

	Screening		Study Days														Discharge	Follow-up/ED	Comments
Procedure	**-28 to -2 days prior to Day 1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Day 16**	**~10 days after last dose**	
Physical Examination	X	X			Predose													X		After screening, medical assessment is performed only to include medical review and targeted examination, as appropriate.
12-Lead ECG	X		Predose		X	X				X					X	X		X		Single; all at predose for morning dose only.
AE/Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Lasmiditan and Metabolite PK Samples			Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h	24, 36 h	48 h											Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24, 36 h	48 h		
Topiramate PK Samples															Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h	Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h				Time points at morning dose only.
Genetic Sample		X																		

Abbreviations: BID = twice daily; BP = blood pressure; CRU = clinical research unit; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; h = hour; min = minutes; PK = pharmacokinetics; QD = once daily.

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 serotonin (5- hydroxytryptamine$_{1F}$) receptor agonist being developed for the acute treatment of migraine.

Topiramate taken daily is indicated for prophylaxis of migraine and may be used concomitantly with lasmiditan in the intended patient population. As such, it is important to understand potential interactions between drugs commonly used in treating migraine, specifically, whether co-administration of such agents results in an increased safety risk or any change in the exposure to either (or both). Very common adverse events (AEs) (≥1/10) associated with topiramate include dizziness, somnolence, paresthesia, nausea, and fatigue (Topiramate US Prescribing Information [https://www.topamax.com/files/topamax.pdf]). Given the occurrence of similar AEs observed following administration of single doses of lasmiditan as documented in Section 3.2, it is important to understand the tolerability when both are co-administered.

Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine. Six metabolites have been identified in humans, none of which constitutes more than 5% of an administered dose. The metabolites are formed via hydroxylation, hydrolysis, and glucuronidation. In vitro studies indicate that topiramate does not inhibit enzyme activity for cytochrome P450 (CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4/5 isozymes. In vitro studies indicate that topiramate is a mild inhibitor of CYP2C19 and a mild inducer of CYP3A4 (Topiramate US Prescribing Information [https://www.topamax.com/files/topamax.pdf]).

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. Ketone reduction 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.

Although the probability of a pharmacokinetic (PK) drug-drug interaction between lasmiditan and topiramate is considered very low based on the low inhibitory potential of both drugs and their diverse elimination pathways, a study of their PK interaction is being conducted as a secondary endpoint to the safety and tolerability of both drugs because of the likelihood for concomitant use in clinical practice.

3.2. Background

Across the completed Phase 1, 2, and 3 clinical studies, doses of 0.1 to 400 mg of lasmiditan were evaluated in healthy subjects or patients with migraine. To date, lasmiditan has been administered to 230 healthy subjects and to 1632 patients with migraine. Compared with placebo, the most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) included dizziness, paresthesia, somnolence, fatigue, lethargy, and nausea. The majority of these

TEAEs were mild or moderate in severity and none led to subject withdrawal. One patient experienced a serious adverse event (SAE) of dizziness that was moderate in severity (lasmiditan 200 mg).

Oral tablet doses of lasmiditan up to 400 mg 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 in healthy subjects, no clinically significant changes in blood pressure, heart rate, or 12-lead ECG were observed at the 100- or 400-mg single-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 intersubject variability in exposure was observed across doses (% coefficient of variation up to 61% and 45% for maximum observed drug concentration [C_{max}] and area under the concentration versus time curve [AUC], respectively). Co-administration of lasmiditan with a high-fat diet led to a delay in median time of maximum observed drug concentration (t_{max}) value by approximately 1 hour and a modest (~20%) increase in lasmiditan C_{max} and AUC values, relative to that under fasted conditions.

3.3. Benefit/Risk Assessment

The primary objective of this study is to evaluate the safety and tolerability of a single dose of lasmiditan in combination with topiramate in healthy subjects. There is no anticipated therapeutic benefit for the subjects.

No clinically significant safety or tolerability concerns have been identified in subjects to date for lasmiditan up to the highest single oral dose given (400 mg). Dosing of lasmiditan in this study will be conducted in an inpatient setting, and subjects will be monitored in the clinical research unit (CRU) for at least 48 hours after dosing.

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

Topiramate is a marketed drug and will be administered within a dose titration regimen that has been tolerated in previous PK studies in healthy subjects (e.g. Bialer et al. 2013; Manitpisitkul et al. 2014a,b).

More detailed information about the known and expected benefits and risks of topiramate may be found in the following: 2017 US Prescribing Information.

4. Objectives and Endpoints

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

Table LAHT.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the safety and tolerability of a single dose of lasmiditan in combination with topiramate in healthy subjects.	A summary of the number of treatment-emergent adverse events and serious adverse events
Secondary To evaluate the pharmacokinetics of lasmiditan alone and in combination with topiramate in healthy subjects. To evaluate the pharmacokinetics of topiramate alone and in combination with lasmiditan.	C_{max}, t_{max}, AUC(0-tlast) and AUC(0-∞) C_{max}, t_{max}, and AUC_{τ}
Exploratory To evaluate the pharmacokinetics of lasmiditan metabolites alone and in combination with topiramate in healthy subjects.	C_{max}, t_{max}, AUC(0-tlast), and AUC(0-∞)

Abbreviations: AUC(0-tlast) = 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; AUC_{τ} = area under the concentration versus time curve during 1 dosing interval; C_{max} = maximum observed drug concentration; t_{max} = time to C_{max}.

5. Study Design

5.1. Overall Design

This is a Phase 1, parallel, placebo-controlled, fixed-sequence study with open-label administration of topiramate and investigator- and subject-blind administration of lasmiditan/placebo conducted in healthy subjects.

Subjects will be admitted to the CRU on Day -1 and are expected to remain a resident until all assessments are completed on Day 16; however, subjects may be allowed to leave the CRU at the discretion of the investigator.

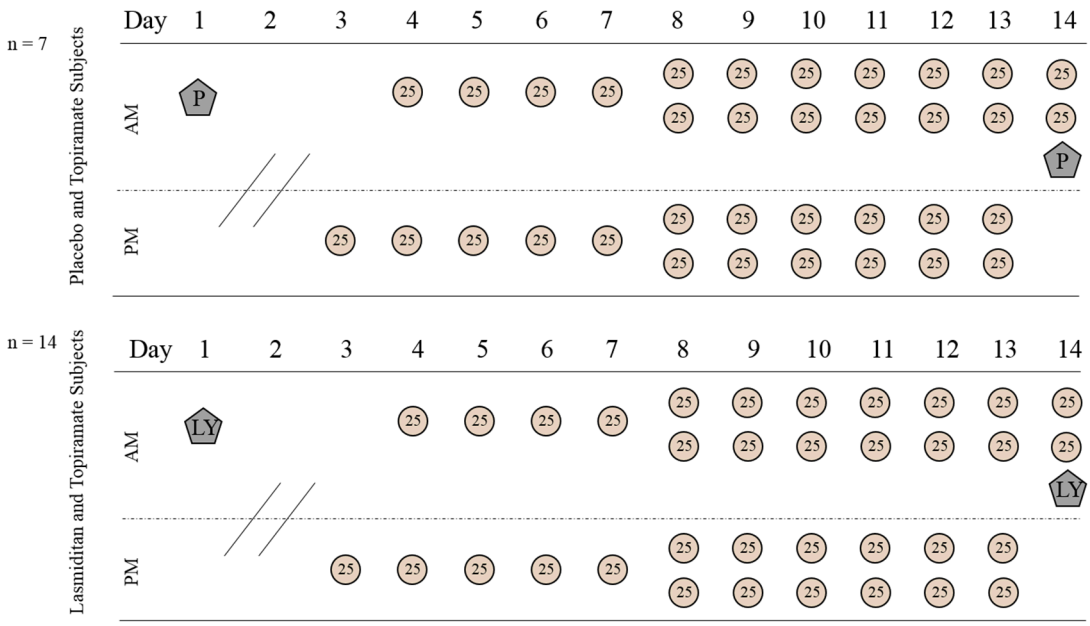
Study governance considerations are described in detail in Appendix 3.

Lasmiditan and topiramate doses will be administered at the CRU. Subjects will be randomly assigned in a 2:1 ratio to receive lasmiditan or placebo on both lasmiditan dosing days (Days 1 and 14). A single oral dose of study drug (200-mg lasmiditan or placebo) will be administered in the morning on Day 1. After lasmiditan wash-out, topiramate will be titrated up to 100 mg on Days 3 to 13. On Day 14, 1 oral dose of lasmiditan 200 mg or placebo will be co-administered with the final topiramate dose (50 mg) in the morning.

Blood sampling for PK assessment will be conducted predose and at time points up to 48 hours postdose on Days 1 and 14 for the measurement of plasma concentrations of lasmiditan and its metabolites. Blood samples will also be collected predose and up to 12 hours postdose on Days 13 and 14 for the measurement of plasma concentrations of topiramate.

A follow-up visit will take place at least 10 days following co-administration of lasmiditan and topiramate (Day 14).

Figure LAHT.1 illustrates the study design.



Abbreviations: LY = lasmiditan (200 mg); n = number of subjects in each group; P = placebo.
Symbols: "25" inside a circle = one 25-mg tablet of topiramate; gray pentagon = lasmiditan dose or placebo.

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

5.2. Number of Participants

Approximately 30 subjects may be enrolled so that at least 21 subjects complete the study. For purposes of this study, a subject completes the study when all scheduled 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 subject.

5.4. Scientific Rationale for Study Design

Subjects will be randomly assigned to 1 of 2 treatment arms. Treatment arms run in parallel and both receive the same topiramate dosing schedule. One treatment arm will receive lasmiditan (200 mg) on Days 1 and 14 when the other receives a lasmiditan placebo to control for observed AEs.

The study has a double-blind (subject- and investigator-blind), fixed-sequence design in which each subject receives lasmiditan or placebo alone, topiramate alone, and lasmiditan or placebo co-administered with topiramate, allowing each subject to act as his/her own control for safety and PK comparisons. A single 200-mg dose of lasmiditan was selected as it is the highest

potential recommended dose for lasmiditan. The washout period between lasmiditan doses of 14 days is considered sufficient based on the half-life of lasmiditan of approximately 4 to 6 hours. Topiramate will be administered using a titration schedule over a period of 12 days to aid tolerability, with a single dose of lasmiditan or placebo co-administered on the final day, to ensure that topiramate concentrations are at steady state at the time of lasmiditan or placebo dosing.

5.5. Justification for Dose

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

As described in the label, topiramate is initiated at 25 mg/day (Day 3), increased to 50 mg/day (Days 4 to 7), and maintained at 100 mg/day (Days 8 to 13). The recommended dosage for migraine prophylaxis is 100 mg/day (Topiramate US Prescribing Information [https://www.topamax.com/files/topamax.pdf]). Similar topiramate titration schedules to reach steady state in healthy subjects demonstrate acceptable safety profiles (Bialer et al. 2013; Manitpisitkul et al. 2014a) and are generally well tolerated (Manitpisitkul et al. 2014b).

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. Subjects who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

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

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

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

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

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

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

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

6.2. Exclusion Criteria

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

[8] are CRU 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 (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study.

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

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

[13] have participated (dosed with IP [lasmiditan or placebo]), within the past 30 days, in a clinical study involving an IP. If the previous IP 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 an abnormal supine blood pressure, defined as systolic blood pressure <90 or >140 mmHg or diastolic blood pressure <60 or >90 mmHg at screening. Repeat assessments may be performed to confirm eligibility.

[16] have a significant history of or current cardiovascular, respiratory (including bronchospasm or bronchial asthma, or chronic obstructive airways disease), hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study medication; or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable.

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

[18] have known or ongoing psychiatric disorders considered clinically significant by the investigator or demonstrate suicidal ideation on the Columbia Suicide Severity Rating Scale (C-SSRS).

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

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

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

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

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

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

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

[26] have an average weekly alcohol intake that exceeds 21 units per week (males up to the age of 65 years) and 14 units per week (females), or are unwilling to stop alcohol consumption 48 hours prior to dosing until the completion of the study (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).

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

[28] have current or a history of orthostatic hypotension (>20-mmHg drop in systolic blood pressure, or >10-mmHg drop in diastolic blood pressure) with or without dizziness and/or syncope at screening or admission to the CRU upon repeat testing.

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

[30] have an estimated glomerular filtration rate using Modification of Diet in Renal Disease <60 mL/min/1.73 m^2.

[31] have a history of glaucoma.

[32] have a history of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption.

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

On intensive PK sampling days (Days 1, 13, and 14), subjects will abstain from water 1 hour before and after dosing (except for water given with the dose). Subjects will fast on these mornings for a minimum of 8 hours predose. Subjects will remain fasting for 3 hours postdose, at which time a meal will be served.

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

6.3.2. Caffeine, Alcohol, and Tobacco

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

Alcohol – Subjects will not consume alcohol for 48 hours prior to dosing, and while resident at the CRU.

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

6.3.3. Activity

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

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

Table LAHT.2 shows the treatment regimens for lasmiditan and topiramate.

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

Table LAHT.2. Treatments Administered

Treatment Name	Lasmiditan LY573144	Lasmiditan Placebo	Topiramate
Dosage Formulation	Film-coated tablet	Film-coated tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s)	(1 × 200-mg) tablet/ 200-mg lasmiditan	NA	(1 × 25-mg) tablet/ 25-mg topiramate (2 × 25-mg) tablet/ 50-mg topiramate
Route of Administration	Oral	Oral	Oral

Abbreviation: NA = not applicable.

The dosing schedule is as follows:

- Day 1: 1 oral dose of lasmiditan (1 × 200-mg tablet or placebo) in the morning

Two days following the initial lasmiditan dose, subjects in the CRU will be administered the following topiramate doses:

- Day 3: starting dose of a single 25-mg tablet
- Days 4 to 7: 2 oral doses of a single 25-mg tablet separated by approximately 12 hours
- Days 8 to 13: 2 oral doses of 50 mg (2 × 25-mg tablets) each separated by approximately 12 hours
- Day 14: Final topiramate dosing (2 × 25-mg tablets) will be co-administered with 1 oral dose of lasmiditan (1 × 200-mg tablet or placebo) in the morning

The investigator or designee is responsible for

- explaining the correct use of the IP(s) to the subject
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensation and collection
- and returning all unused medications to Lilly or its designee at the end of the study

Note: In some cases, the CRU 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.

The study site will obtain topiramate.

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

7.2. Method of Treatment Assignment

The sponsor (or designee) will be responsible for generating each of the randomization schedules and distributing them directly to the CRU pharmacist.

7.2.1. Selection and Timing of Doses

Doses of topiramate will be administered at approximately the same times on each dosing day (every 12 hours) except for Day 3 and Day 14 when only 1 dose is administered. On Day 14, topiramate (50 mg) should be co-administered with lasmiditan (200 mg). The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

7.3. Blinding

Investigator and subject blinding of lasmiditan will be maintained throughout the conduct of the study as described in the separate Blinding Plan. Topiramate will be administered open-label.

Emergency codes will be available to the pharmacy. A code, which reveals the lasmiditan treatment group 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

Only participants enrolled in the study may receive IP or study materials, and only authorized CRU staff may supply or administer IP. All IPs 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 CRU 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 IP will be administered at the CRU, and documentation of treatment administration will occur at the CRU.

7.7. Concomitant Therapy

In general, concomitant medication should be avoided; however, acetaminophen (1 g, maximum 4 g/24 hours) may be administered at the discretion of the investigator for treatment of headache, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist or CRP. Hormone replacement therapy is allowed per the inclusion criteria. 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.

8.1. Discontinuation from Study Treatment

Discontinuation of the IP for abnormal liver test results **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 sustained for more than 2 weeks or
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio >1.5 or
- 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 TBL >2X ULN
- ALP >2.5 ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist/CRP 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 to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an IP 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

  - if the subject, 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

- Subject Decision
  - the subject, or legal representative, requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the CRU. 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 IP or the study, or that caused the subject to discontinue the IP 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, CRU personnel will record, via eCRF, the occurrence and nature of each subject's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

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

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly CRP/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 subject has signed informed consent and has received IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, 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 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 IP) 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 IP or procedure. Lilly has procedures that

will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

9.3.1. Overdose of Lasmiditan

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

Refer to the IB.

9.3.2. Overdose of Topiramate

In the event of a topiramate overdose, the subject should receive appropriate supportive care according to the approved product label for advice on overdose.

Refer to the 2017 US Prescribing Information (Topiramate US Prescribing Information [https://www.topamax.com/files/topamax.pdf]).

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).

9.4.2. Vital Signs

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

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

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

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

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

9.4.3. Electrocardiograms

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

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

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

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

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

9.4.4. Columbia Suicide Severity Rating Scale

The C-SSRS (Posner 2007; Posner et al. 2007a,b) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The C-SSRS and a corresponding Self-Harm Supplement Form will be administered according to the Schedule of Activities by appropriately trained site personnel. Any significant change would need to be referred to a psychiatrist.

If the investigator determines that suicide-related behaviors have occurred, the Lilly self-harm follow-up form will be used to collect additional information to allow for a more complete assessment of these behaviors. As noted above, subjects with any clinically significant change, as determined by the investigator, will be referred to a psychiatrist.

9.4.5. Neurological Examinations

Neurological examinations will be performed as indicated in the Schedule of Activities.

The neurological examination will include observation for tremors and testing of ocular movements, finger-to-nose and heel-to-shin testing, rapid alternating movements, tandem walking, strength testing, and muscle stretch (deep) reflexes. An experienced clinician will conduct the neurological examination. Please see Appendix 6 for a description of the techniques used.

Positive significant findings (such as nystagmus, dystaxia, ataxia, irregular alternating movements, and hyperreflexia) on neurological examination of oculomotor testing, tandem walking, heel-to-shin, rapid alternating movements, finger-nose coordination, and muscle stretch (deep) reflexes will be recorded as preexisting conditions or AEs. A clinically significant change from baseline or clinically significant new findings should be a consideration for discontinuation of study drug.

9.4.6. 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.

9.4.6.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly 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
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests

- patient/subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of lasmiditan and its metabolites. Similarly, at times specified in the Schedule of Activities, 2 mL of venous blood samples will be collected to determine the plasma concentrations of topiramate. 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 tandem-mass spectrometry (LC-MS/MS) method. Analyses of samples collected from subjects who received placebo are not planned.

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

Bioanalytical samples collected to measure IP 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.

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 or topiramate 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

Not applicable.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 30 subjects will be enrolled, so that at least 21 subjects complete the study. Subjects will be randomized in a 2:1 ratio of lasmiditan 200 mg:placebo. The sample size is customary for Phase 1 studies evaluating safety and tolerability, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but who do not complete Day 14 treatment may be replaced to ensure that enough subjects complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The subjects' age, sex, weight, height, BMI, race, and other demographic characteristics will be recorded and summarized.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least 1 dose of lasmiditan or topiramate 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 IP and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

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

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, neurological examinations, and C-SSRS. The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan and its metabolites, and topiramate will be calculated using 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 from zero to infinity for lasmiditan and its metabolites on Days 1 and 14, and C_{max}, t_{max}, and AUC during 1 dosing interval for topiramate on Days 13 and 14. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to determine the impact of topiramate co-administration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with fixed effects for treatment (lasmiditan co-administered with topiramate [Day 14; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

A similar analysis will be performed to determine the impact of co-administration of a single dose of lasmiditan on the steady-state PK of topiramate. The model will include the following treatments: topiramate co-administered with lasmiditan (Day 14; test treatment) versus topiramate alone (Day 13; reference treatment).

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

Additional analyses may be performed, as warranted.

11. References

Bialer M, Shekh-Ahmad T, Braun T, Halorsen M. Comparative steady-state pharmacokinetic evaluation of immediate-release topiramate and USL255, a once-daily extended-release topiramate formulation. *Epilepsia*. 2013;54(8):1444-1452.

Manitpisitkul P, Curtin CR, Shalayda K, Wang S, Ford L, Heald D. Pharmacokinetic interactions between topiramate and diltiazem, hydrochlorothiazide, or propranolol. *Clin Pharmacol Drug Dev*. 2014a;3(5):378-387.

Manitpisitkul P, Curtin CR, Shalayda K, Wang S, Ford L, Heald D. Pharmacokinetic interactions between topiramate and pioglitazone and metformin. *Epilepsy Res*. 2014b;108(9):1519-1532.

Posner K. State of the science: measurement of suicidal adverse events and the Columbia suicide severity rating scale. Boca Raton, FL: NCDEU; 2007.

Posner K, Melvin GA, Stanley B, Oquendo MA, Gould M. Factors in the assessment of suicidality in youth. *CNS Spectr*. 2007a;12(2):156-162.

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*. 2007b;165(7):1035-1043.

Topiramate US Prescribing Information resource page. Topomax web site. May 2017. Available at: https://www.topamax.com/files/topamax.pdf. Accessed June 15, 2017.

Appendix 1. Abbreviations and Definitions

Term	Definition
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
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested 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
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	cytochrome P450
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
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
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 subject, to the subject's participation in the clinical study.
non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to subjects and used in accordance with the protocol, such as concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PK	pharmacokinetic(s)
QTc	corrected QT interval
randomize	The process of assigning subjects/patients to an experimental group on a random basis.
SAE	serious adverse event

screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
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 (BUN)
Differential WBC absolute counts and % of	Total protein
Neutrophils	Albumin
Lymphocytes	Reflex total bilirubin
Monocytes	Alkaline phosphatase (ALP)
Eosinophils	Aspartate aminotransferase (AST)
Basophils	Alanine aminotransferase (ALT)
	Creatinine
	Gamma-glutamyl transferase (GGT)
Urinalysis	
Specific gravity	
pH	
Protein	
Glucose	Ethanol testing[b]
Ketones	Urine drug screen[b]
	Urine pregnancy test
Bilirubin	Hepatitis B surface antigen[a]
Urobilinogen	Hepatitis C antibody[a]
Blood	HIV[a]
Nitrite	Serum pregnancy test (females only)[a]
Urine microscopic (if positive result for blood)	FSH (females only, if applicable)[c]

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

[a] Performed at screening only.

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

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

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

- ensuring that the subject understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each subject or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of IP.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Ethical Review

The investigator or appropriate local representative must give assurance that the ERB was properly constituted and convened as required by International Council for 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 International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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

Protocol Signatures

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

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the CRU, 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/patient personal information collected will be provided in a written document to the subject/patient by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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-LAHT Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12.5	5	62.5
Lasmiditan and metabolite pharmacokinetics[b]	3	27	81
Topiramate pharmacokinetics[b]	2	20	40
Pharmacogenetics	10	1	10
Total			238.5
Total for clinical purposes rounded up to the nearest 10 mL			240

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

[b] Includes a potential 3 additional samples.

Appendix 6. Neurological Examinations

Tests for Dysfunction on Neurological Examination	
Abnormality	**Method of Examination**
Gait dystaxia	Free walking for broad-based gait Tandem walking
Nystagmus	Have patient follow your finger through fields of gaze
Irregular alternating movements	Thigh slapping test
Arm dystaxia	Finger-to-nose
Leg dystaxia	Heel-to-shin
Scapular winging	Strength testing
Hyperreflexia	Muscle stretch (deep) reflexes

Dystaxia = incoordination of intentional movements

Neurological Examination

1) Test station (stance) and gait:

- Inspect the patient for swaying when standing and for dystaxia of gait.
- Ask the patient to stand with feet together.
- Ask the patient to take 6 steps along a straight line, walking heel to toe (tandem walking).

2) Test eye movements:

- Observe spontaneous eye movements.
- Observe the patient's eyes as they pursue the examiner's finger as it moves from side-to-side and up and down through the full range of ocular movements.

3) Test rapid alternating movements:

- Thigh-slapping test. Test each hand separately.
- Demonstrate the action to the patient by lightly slapping your own thigh, alternating first with the palm and then with the back of the hand as rapidly and rhythmically as possible, making an audible sound with each slap.
- Instruct the patient to make actions that sound exactly like yours.

4) Test arm movement:

- Finger-to-nose test. Ask the patient to extend his arms out in front.
- Instruct him to place his index finger on the tip of his nose by moving his finger in slowly, and placing the tip of his finger exactly on the tip of his nose, trying not to miss.

- Inspect for intention tremor of the movement in progress, and the precision with which the patient touches the tip of his nose.
- If uncertain of the result, have the patient alternatively touch his nose, your finger, and his nose several times.

5) Test leg movement:

- Heel-to-shin test. The patient is sitting or supine.
- Instruct the patient to place one heel precisely on the opposite knee and run the heel in a straight line precisely down the shin.

6) Strength testing:

- Shoulder girdle. Try to press the patient's arms down after he or she abducts them to shoulder height. Look for scapular winging.
- Upper extremities. Test the biceps, triceps, wrist dorsiflexors, and grip. Test strength of finger abduction and extension.
- Lower extremities. Test hip flexors, abductors and adductors, knee flexors, foot dorsiflexors, invertors, and evertors. Have patient do a deep knee bend to test knee extension.
- Grade strength on a 0 to 5 scale.

7) Muscle stretch (deep) reflexes:

- Biceps
- Triceps
- Quadriceps (knee reflex)
- Triceps surae (ankle jerk)
- Grade 0 to 4+

Positive significant findings (such as nystagmus, dystaxia, ataxia, and irregular alternating movements*) on neurological examination of oculomotor testing, tandem walking, heel-to-shin, rapid alternating movements, finger-nose coordination and muscle stretch (deep) reflexes will be recorded as pre-existing conditions or adverse events. Increase in severity from baseline or new findings should be a consideration for discontinuation of study drug.

* Enter "clumsiness" for irregular alternating movements on the eCRF as the pre-existing condition or adverse event.

Appendix 7. Protocol Amendment H8H-MC-LAHT(c) Summary Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate in Healthy Subjects

Overview

Protocol H8H-MC-LAHT, Safety, Tolerability, and Pharmacokinetics of Lasmiditan when Co-administered with Topiramate 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.

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:

Safety parameters that will be assessed include safety laboratory parameters, vital signs, neurological examination, Columbia Suicide Severity Rating Scale, and 12-lead electrocardiogram parameters. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameter estimates for lasmiditan, its metabolites, and topiramate will be calculated using standard noncompartmental methods of analysis. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

Pharmacokinetic parameters will be evaluated to determine the impact of topiramate co-administration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and area under the concentration versus time curve parameters will be evaluated in a linear mixed-effects model with fixed effects for treatment (lasmiditan co-administered with topiramate [Day 14; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

A similar analysis will be performed to determine the impact of co-administration of a single dose of lasmiditan on the steady-state PK of topiramate. The model will include the following treatments: topiramate co-administered with lasmiditan (Day 14; test treatment) versus topiramate alone (Day 13; reference treatment).

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

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAHT

	Screening		Study Days														Discharge	Follow-up/ED	Comments
Procedure	**-28 to -2 days prior to Day 1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**Day 16**	**~10 days after last dose**	
Lasmiditan and Metabolite PK Samples			Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 h	24, 36 h	48 h											Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24, 36 h	48 h		

4. Objectives and Endpoints

Table LAHT.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the safety and tolerability of a single dose of lasmiditan in combination with topiramate in healthy subjects.	A summary of the number of treatment-emergent adverse events and serious adverse events
Secondary To evaluate the pharmacokinetics of lasmiditan alone and in combination with topiramate in healthy subjects. To evaluate the pharmacokinetics of topiramate alone and in combination with lasmiditan.	C_{max}, t_{max}, AUC(0-tlast) and AUC(0-∞) C_{max}, t_{max}, and AUC_{τ}
Exploratory To evaluate the pharmacokinetics of lasmiditan metabolites alone and in combination with topiramate in healthy subjects.	C_{max}, t_{max}, AUC(0-tlast), and AUC(0-∞)

Abbreviations: AUC(0-tlast) = 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; AUC_{τ} = area under the concentration versus time curve during 1 dosing interval; C_{max} = maximum observed drug concentration; t_{max} = time to C_{max}.

5.1. Overall Design

This is a Phase 1, parallel, placebo-controlled, fixed-sequence study with open-label administration of topiramate and investigator- and subject-blind administration of lasmiditan/placebo conducted in healthy subjects.

Subjects will be admitted to the CRU on Day -1 and are expected to remain a resident until all assessments are completed on Day 16; however, subjects may be allowed to leave the CRU at the discretion of the investigator.

Study governance considerations are described in detail in Appendix 3.

Lasmiditan and topiramate doses will be administered at the CRU. Subjects will be randomly assigned in a 2:1 ratio to receive lasmiditan or placebo on both lasmiditan dosing days (Days 1 and 14). A single oral dose of study drug (200-mg lasmiditan or placebo) will be administered in the morning on Day 1. After lasmiditan wash-out, topiramate will be titrated up to 100 mg on Days 3 to 13. On Day 14, 1 oral dose of lasmiditan 200 mg or placebo will be co-administered with the final topiramate dose (50 mg) in the morning.

Blood sampling for PK assessment will be conducted predose and at time points up to 48 hours postdose on Days 1 and 14 for the measurement of plasma concentrations of lasmiditan and its metabolites. Blood samples will also be collected predose and up to 12 hours postdose on Days 13 and 14 for the measurement of plasma concentrations of topiramate.

A follow-up visit will take place at least 10 days following co-administration of lasmiditan and topiramate (Day 14).

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of lasmiditan and its metabolites. Similarly, at times specified in the Schedule of Activities, 2 mL of venous blood samples will be collected to determine the plasma concentrations of topiramate. 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 tandem-mass spectrometry (LC-MS/MS) method. Analyses of samples collected from subjects who received placebo are not planned.

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

Bioanalytical samples collected to measure IP 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.

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan and its metabolites, and topiramate will be calculated using 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 from zero to infinity for lasmiditan and its metabolites on Days 1 and 14, and C_{max}, t_{max}, and AUC during 1 dosing interval for topiramate on Days 13 and 14. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be evaluated to determine the impact of topiramate co-administration on the PK of a single dose of lasmiditan and its metabolites. Log-transformed C_{max} and AUC parameters will be evaluated in a linear mixed-effects model with fixed effects for treatment (lasmiditan co-administered with topiramate [Day 14; test treatment] versus lasmiditan alone [Day 1; reference treatment]), and a random effect for subject. The treatment differences will be back-transformed to present the ratios of geometric means and the corresponding 90% confidence interval (CI).

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-LAHT Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	45	1	45
Clinical laboratory tests[a]	12.5	5	62.5
Lasmiditan and metabolite pharmacokinetics[b]	3	27	81
Topiramate pharmacokinetics[b]	2	20	40
Pharmacogenetics	10	1	10
Total			238.5
Total for clinical purposes rounded up to the nearest 10 mL			240

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

[b] Includes a potential 3 additional samples.

Leo Document ID = 9147c1ba-6644-46bd-a6c6-a9340b641595

Approver: PPD
Approval Date & Time: 19-Oct-2017 17:11:26 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 20-Oct-2017 08:36:56 GMT
Signature meaning: Approved