Protocol H8H-MC-LAIC(a)

Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects

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Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects

Confidential Information

Lasmiditan (LY573144)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Clinical Pharmacology Protocol Approved by Lilly: 09 Aug 2018

Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

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1. Protocol Synopsis

Title of Study:
Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects

Rationale:
Lasmiditan is a highly selective and potent agonist of the 5-hydroxytryptamine (5-HT)1F receptor that is being developed as a neurally acting treatment for migraine.

This study is the first clinical evaluation of single and multiple oral doses of lasmiditan in Chinese subjects, and will facilitate subsequent clinical trials in Chinese patients. Characterization of the safety and pharmacokinetics (PK) of lasmiditan in Chinese subjects is essential for further clinical development in China.

Objectives/Endpoints:

Objectives	Endpoints
Primary To evaluate the PK of single and multiple doses of lasmiditan in healthy Chinese subjects.	AUC(0-∞) [single-dose only], AUC(0-τ) C_{max}, and t_{max}.
Secondary To explore the safety and tolerability of single and multiple oral doses of lasmiditan in healthy Chinese subjects.	Incidence of SAEs and TEAEs.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero extrapolated to infinity; AUC(0-τ) = area under the concentration versus time curve over a dosing interval; C_{max} = maximum observed plasma concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time of maximum observed plasma concentration.

Summary of Study Design:

Study H8H-MC-LAIC is an investigator- and subject-blinded, randomized, placebo-controlled study in healthy Chinese subjects. The study will evaluate the safety, tolerability, and PK of lasmiditan following single and multiple oral doses of 50, 100, and 200 mg.

Treatment Arms and Planned Duration for an Individual Subject:

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

Subjects will be enrolled into 1 of 3 cohorts. All subjects will be admitted to the clinical research unit (CRU) on Day -1. Each subject will receive a single dose of lasmiditan or placebo on Day 1 and multiple once-daily doses of lasmiditan or placebo on Days 4 to 10 of the study. Subjects will discharge from the CRU on Day 12 and attend a follow-up visit approximately 7 to 10 days following their final dose of investigational product (IP).

The planned study duration for each subject will be up to 50 days.

Number of Subjects:

Up to 36 subjects (12 subjects per cohort) may be enrolled and randomized so that approximately 8 subjects per cohort, who receive lasmiditan, complete the study.

Statistical Analysis:

Safety parameters that will be assessed include safety lab parameters and vital signs. The parameters will be listed and summarized using descriptive statistics as appropriate.

Pharmacokinetic parameter estimates for lasmiditan and metabolites M7, M8, (S,R)-M18, and (S,S)-M18 will be calculated by standard noncompartmental methods of analysis. Trough concentrations of lasmiditan and its metabolites will be evaluated graphically and/or descriptively for achievement of steady-state.

Log-transformed C_{max} and AUC parameters (AUC[0-∞] for Day 1 and AUC[0-τ] for Day 10) will be evaluated using a power model (where the log of the dose will be an explanatory variable) to estimate ratios of dose-normalized geometric means and the corresponding 90% confidence intervals (CIs). The estimated ratio between the highest and lowest doses will be used to assess dose proportionality. The intersubject coefficient of variation will be derived.

2. Schedule of Activities

Study Schedule Protocol H8H-MC-LAIC

	Screening	Day									**FU/ ED**	**Comments**
Procedure	D-28 to D-2	-1	1	2	3	4	5 to 9	10	11	12		FU approximately 7 to 10 days post final dose.
Informed Consent	X											
Subject Admission to CRU		X										
Subject Discharge from CRU										X		
Lasmiditan or Placebo Administration			X			X	X	X				Approximately 72 hours between the first (D1) and second (D4) lasmiditan/placebo doses.
Medical History	X											
Urine Drug Screen	X	X										
Alcohol test	X	X										
Height	X											
Weight	X	X									X	
Single Vital Signs (supine)	X		P, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h		P, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h (D5)	P, 0.5, 1, 2, 2.5, 3, 4, 6, 8, 12 h	24 h		X	Time points relative to dosing on D1, D4, and D10. Vital signs may be performed at other times as clinically indicated, determined by the investigator.
Single Orthostatic Vital Signs	X		P, 2 h	24 h		P, 2 h	24 h (D5)	P, 2 h	24 h			Time points relative to dosing on D1, D4, and D10. Vital signs may be performed at other times as clinically indicated, determined by the investigator.
Clinical Laboratory Tests	X	X	P			P		P		X	X	See Appendix 2, Clinical Laboratory Tests, for details.

	Screening	Day									**FU/ ED**	**Comments**
Procedure	D-28 to D-2	-1	1	2	3	4	5 to 9	10	11	12		FU approximately 7 to 10 days post final dose.
HIV/Hepatitis Tests	X											See Appendix 2, Clinical Laboratory Tests, for details.
Pregnancy Test	X	X									X	Female subjects of childbearing potential only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed at admission and at FU.
FSH	X											Postmenopausal females only.
Physical Examination	X	X			X					X	X	After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.
Single 12-Lead ECG	X		P, 2, 4 h	24 h		P, 2, 4 h	24 h (D5)	P, 2, 4 h	24 h		X	Time points relative to dosing on D1, D4, and D10.
C-SSRS and Lilly Self-Harm Supplement	X	X								X	X	C-SSRS "Baseline" questionnaire to be used at screening, all other time points use "Since Last Visit" questionnaire.
Adverse Event Review		X	X	X	X	X	X	X	X	X	X	
Plasma Samples for Lasmiditan and Metabolite Pharmacokinetics			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24, 36 h	48 h	P	P	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24, 36 h	48 h		Time points relative to dosing on D1, D4, and D10. Predose samples to be taken on D5 to D9 for assessment of steady-state.

Abbreviations: CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle-stimulating hormone; FU = follow-up; HIV = human immunodeficiency virus; P = predose.

Note: if multiple procedures take place at the same time point, the following order of the procedure should be use: ECG, vital signs, and venipuncture.

3. Introduction

Lasmiditan (LY573144) is being developed by Eli Lilly and Company (Lilly) for the acute treatment of migraine attacks, with or without aura, in adults. This molecule has also been developed by CoLucid Pharmaceuticals, Inc. as COL-144. Full details of the preclinical and clinical safety and tolerability data are contained in the Investigator's Brochure (IB).

3.1. Study Rationale

Lasmiditan is a highly selective and potent agonist of the 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor that is being developed as a neurally acting treatment for migraine.

This study is the first clinical evaluation of single and multiple doses of lasmiditan in Chinese subjects, and will facilitate subsequent clinical trials in Chinese patients. Characterization of the safety and pharmacokinetics (PK) of lasmiditan in Chinese subjects is essential for further clinical development in China.

3.2. Background

Lasmiditan has a chemical structure and pharmacological profile that is distinct from triptans, which are the current standard of care for the treatment of acute migraine. It does not contain the indole group found in all triptans, but instead has a pyridinoyl-piperidine scaffold that is unique to antimigraine medications. Lasmiditan is a low-molecular-weight agonist of the 5-HT_{1F} receptor with a nonvascular and primarily neural mechanism of action. It has a high affinity for the human 5-HT_{1F} receptor and a >470-fold selectivity for the human 5-HT_{1F} receptor relative to the 5-HT_{1B} receptor.

Lasmiditan doses of 0.1 to 400 mg have been evaluated in healthy subjects or patients with migraine across completed Phase 1, 2, and 3 clinical studies. Cumulatively through 05 March 2018, a total of 3948 subjects/patients have received lasmiditan. The most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) in the 2 Phase 3 placebo-controlled studies, in which patients treated 1 migraine attack with oral lasmiditan (50, 100, or 200 mg) or placebo, were dizziness, paresthesia, somnolence, fatigue, lethargy, and nausea, and the majority were mild or moderate in severity. Safety and tolerability in healthy subjects were similar up to the highest dose of 400 mg administered as a single and multiple (once daily for 7 days) dose, with tiredness, drowsiness, dizziness, and paresthesia being the most frequently reported adverse events (AEs). The majority of these were mild in severity, and none were severe.

Following dose administration of a single oral tablet to healthy subjects, lasmiditan was absorbed with a median t_{max} of 1.5 to 2.5 hours, and rapidly eliminated with a mean $t_{1/2}$ of approximately 4 hours. Over the clinical dose range of 50 to 200 mg, the mean estimates of lasmiditan C_{max} and AUC(0-∞) increased in a dose-dependent manner that was approximately linear with dose.

Following oral dosing with lasmiditan, up to 16 metabolites, including 3 major metabolites (M7, M8, and M18), were detected in human plasma and urine. These metabolites lacked significant pharmacological activity at the 5-HT_{1F} receptor and were generally considered to be pharmacologically inactive. The relative proportions of metabolites to intact lasmiditan

remained reasonably constant throughout the oral dose range studied and their PK was approximately linear. The half-life of the metabolites ranged from approximately 4.5 to 21 hours.

The characterization of lasmiditan PK in Asian subjects has been limited. Therefore, it is not known whether there are PK differences between subjects of Asian descent, relative to the overall population.

3.3. Benefit/Risk Assessment

Oral doses of lasmiditan up to the highest single and multiple oral dose given (400 mg) were well tolerated in healthy subjects, with no drug-related serious adverse events (SAEs) or withdrawals due to AEs as of 05 March 2018. Lasmiditan caused no significant QT prolongation either at 100 or 400 mg, and no clinically significant changes in clinical laboratory data. Lasmiditan has been associated with transient lowering of heart rate (on average about 8 to 12 bpm). Throughout this study, vital signs will be closely monitored for effects of lasmiditan on heart rate. Although nervous system disorders were commonly reported as AEs, especially at higher dose levels, they were generally mild or moderate in intensity. Dosing of subjects in this study will be conducted in an inpatient setting, and subjects will be monitored in-house for at least 48 hours after the last dose of investigational product (IP).

There is no anticipated therapeutic benefit for the subjects.

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

4. Objectives and Endpoints

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

Table LAIC.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the PK of single and multiple doses of lasmiditan in healthy Chinese subjects.	AUC(0-∞) [single-dose only], AUC(0-τ), C_{max}, and t_{max}.
Secondary To explore the safety and tolerability of single and multiple oral doses of lasmiditan in healthy Chinese subjects.	Incidence of SAEs and TEAEs.
Exploratory To evaluate the PK of metabolites M7, M8, (S,R)-M18, and (S,S)-M18 in healthy Chinese subjects.	AUC(0-∞), C_{max}, and t_{max}.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero extrapolated to infinity; AUC(0-τ) = area under the concentration versus time curve over a dosing interval; C_{max} = maximum observed plasma concentration; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event; t_{max} = time of maximum observed plasma concentration.

5. Study Design

5.1. Overall Design

This study is a Phase 1, investigator- and subject-blinded, randomized, placebo-controlled study in healthy Chinese subjects.

Subjects will be enrolled into 1 of 3 cohorts and receive single and multiple doses of lasmiditan or placebo in a parallel design. Each cohort will comprise 12 subjects (10 lasmiditan:2 placebo) and will be assigned the following doses:

- Cohort 1 = 50 mg lasmiditan (or placebo)
- Cohort 2 = 100 mg lasmiditan (or placebo)
- Cohort 3 = 200 mg lasmiditan (or placebo)

Subjects will be evaluated for study eligibility ≤28 days prior to enrollment. Subjects who fulfill the eligibility criteria will be admitted to the clinical research unit (CRU) on Day -1 (the day before their first dose of lasmiditan or placebo; Section 2).

After randomization on Day 1, IP (lasmiditan or placebo) will be administered orally once on the morning of Day 1 after an overnight fast of at least 8 hours. Following a period of at least 72 hours without IP dosing, subjects will receive multiple once-daily oral doses of IP on Days 4 to 10 (7 days of dosing), after overnight fasts of at least 8 hours prior to each dose. The doses of lasmiditan administered on Days 4 to 10 will be the same dose as that administered on Day 1 for each subject.

Subjects will be discharged from the CRU on Day 12 following completion of all scheduled procedures, as defined in the Schedule of Activities (Section 2), and will attend a follow-up visit approximately 7 to 10 days following final oral dose of IP.

The planned study duration for each subject will be up to 50 days.

Blood samples will be collected for PK analysis. Safety and tolerability will be assessed throughout the study by means of AE review, physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS).

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 36 subjects (12 subjects per cohort) may be enrolled and randomized so that approximately 8 subjects per cohort, who receive lasmiditan, complete the study. For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) 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

A subject- and investigator-blinded, randomized, and placebo-controlled design has been chosen to minimize bias in the safety and tolerability objective of this study.

Single and repeated doses of 50, 100, and 200 mg lasmiditan are considered the planned clinical doses.

Pharmacokinetic sampling time points have been selected to generate PK profiles sufficient to fulfill the study objectives.

Conducting the study in healthy subjects mitigates the potential confounding effects of the disease state, other medical conditions, and concomitant medications in patients. Conducting this study in Chinese subjects will provide PK data for evaluation on ethnic sensitivity of lasmiditan. In addition, it will support the inclusion of Chinese subjects in a future global Phase 3 study with lasmiditan.

It is not considered necessary to conduct safety data reviews of previous cohorts (lower dose levels) prior to dosing the next cohort. The relative dosing of cohorts (parallel or sequential) will therefore be at the discretion of the investigator.

5.5. Justification for Dose

Oral doses of 50, 100, and 200 mg lasmiditan are envisaged to be clinically effective doses for the target population, based on data obtained from previous completed studies.

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, are not permitted.

6.1. Inclusion Criteria

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

[1] are overtly healthy Chinese (all 4 biological grandparents and both biological parents to be of Chinese origin) males or females, as determined by medical history and physical examination

[1a] male subjects will not be subject to any specific contraception requirements

[1b] women of childbearing potential must test negative for pregnancy at screening and on Day -1, and must agree to use 1 highly effective (<1% failure rate) method of contraception or 2 effective methods of contraception during the study and for 30 days following the last dose of IP.

Highly effective methods of contraception include oral contraceptives, implanted contraceptives, or intrauterine devices. Effective methods of contraception include male or female condoms with concomitant use of spermicide, diaphragm with spermicide, or cervical sponges. Barrier methods without the concomitant use of spermicide or the use of male and female condoms as a double-barrier method are not acceptable.

Women of childbearing potential who practice abstinence or are in same-sex relationships, as their preferred and usual lifestyle, must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the purpose of the study, and withdrawal are not acceptable.

[1c] women of non-childbearing potential may participate and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis, or
- postmenopausal, defined as:
    - a woman of at least 50 years of age with an intact uterus, not on hormone therapy, who has had either cessation of menses for at least 1 year or at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone level >40 mIU/mL, or
    - a woman 55 years of age or older, not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea, or
    - a woman of at least 55 years of age with a diagnosis of menopause prior to starting hormone-replacement therapy

[2] are aged between 18 and 65 years, inclusive, at screening

[3] have a body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive

[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] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

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

[9] are Lilly employees or are employees of third-party organizations involved with the study

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

[11] have participated, within the last 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

[12] have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received the IP

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

[14] have a history of, or ECG findings of, clinically significant bradycardia, heart block, tachyarrhythmia, bradyarrhythmia, or have any other abnormality that, in the opinion of the investigator, increases the risk of participating in the study

[15] have an abnormal blood pressure and/or pulse rate as determined clinically significant by the investigator

[16] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data. Examples of excluded conditions include, but are not limited to; hypertension, angina, heart failure, asthma (childhood asthma is acceptable), chronic obstructive airways disease, hepatitis, cirrhosis, renal impairment, diabetes, anemia, migraine, fits, seizures (except febrile convulsions), significant head trauma, surgical resection of bowel (appendectomy is acceptable), or any other condition requiring chronic medication

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

[18] have a recent history of a suicide attempt (30 days within screening visit and any time between screening visit and baseline), evidence of suicide-related thought or behavior as identified by the C-SSRS, or are clinically judged by the investigator to be at risk for suicide

[19] have a history of central nervous system (CNS) conditions such as strokes, transient ischemic attack, 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

[20] regularly use known drugs of abuse and/or show positive findings on drug screening

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

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

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

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

[25] have used or intend to use over-the-counter or prescription medication including herbal medications and Chinese traditional medicine within 14 days prior to admission to the CRU and until discharge from the study (with the exception of hormone-replacement therapy, oral contraceptives, or occasional acetaminophen use)

[26] have donated blood of more than 400 mL within 1 month prior to screening

[27] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption 48 hours prior to admission and throughout the duration 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)

[28] currently use or have a history of drug or alcohol abuse

[29] are smokers of more than 10 cigarettes or e-cigarettes, or 3 cigars or 3 pipes per day, and are unable to refrain from smoking for 48 hours prior to admission to and while resident at the CRU

[30] 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] to [7] define a healthy population that is suitable for evaluation in a Phase 1 study and define the Chinese population for the purposes of this study. The use of lasmiditan in Chinese patients is anticipated, thus this study will specifically examine the PK, safety, and tolerability in Chinese subjects.

Criteria [8] and [9] prevent conflict of interest in study participants. Criteria [10] to [30] predominantly exclude medical conditions, medical intolerances, and concomitant medications that may confound the assessment of study endpoints, or may affect subject or investigative site safety.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Lasmiditan will be administered after an overnight fast of at least 8 hours. Subjects will remain fasting for 3 hours postdose on Days 1 and 10. On Days 2 to 9, a light breakfast will be allowed 1 hour postdose. With the exception of water given with the lasmiditan dose, subjects will abstain from fluid intake for 1 hour before and for 1 hour after dosing.

Standardized meals will be provided at all other times while resident at the CRU.

6.3.2. Caffeine, Alcohol, and Tobacco

Subjects will refrain from consuming xanthine- or caffeine-containing food and drinks from 48 hours prior to admission to the CRU until the end of the study period.

Subjects will refrain from consuming grapefruit and grapefruit-containing products from 7 days prior to admission to the CRU until discharge from the study.

Alcohol consumption is not permitted for 48 hours prior to admission to the CRU and for the duration of the study.

Subjects will refrain from smoking for 48 hours prior to admission to and while resident at the CRU.

6.3.3. Activity

No strenuous exercise is permitted for 48 hours prior to admission to the CRU until discharge from the study.

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

This study involves a comparison of single (Day 1) and repeated (Days 4 to 10) doses of 50, 100, and 200 mg lasmiditan administered orally, with placebo.

Table LAIC.2 shows the treatment regimens at for each cohort.

Table LAIC.2. Treatments Administered

Cohort	Dose level	Number of tablets administered per dose
1	50 mg lasmiditan or placebo	1 x 50-mg tablet
2	100 mg lasmiditan or placebo	1 x 100-mg tablet
3	200 mg lasmiditan or placebo	2 x 100-mg tablet

Tablets of lasmiditan or placebo will be orally administered 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.

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

Each tablet of lasmiditan contains 50 or 100 mg of active ingredient and is provided in a blister. Placebo tablets look identical but contain no active ingredient and will be provided in a similar blister.

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

7.2. Method of Treatment Assignment

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign a blister containing double-blind IP to each subject.

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same times on each day. The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

7.3. Blinding

The investigator and subjects will be blinded to the study treatment assignments.

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events are recorded and reported by the IWRS.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist (CP) or 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 in this study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by sponsor, during transit for all IP received and any discrepancies are reported and resolved before use of the study treatment.

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

7.7. Concomitant Therapy

In general, concomitant medication should be avoided; however, acetaminophen (1g, maximum 3 g/24 hours) may be administered at the discretion of the investigator for treatment of minor AEs. For female subjects, the use of hormone-replacement therapy will be permitted.

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

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Subjects discontinuing from the treatment prematurely for any reason should complete adverse event and other follow-up procedures per Section 2 of this protocol.

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

8.1. Discontinuation from Study Treatment

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

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 × upper limit of normal (ULN)
- ALT or AST >3 × ULN sustained for more than 2 weeks
- ALT or AST >3 × ULN and total bilirubin level (TBL) >2 × ULN or international normalized ratio (INR) >1.5
- ALT or AST >3 × ULN and the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3 × ULN
- ALP >2.5 × ULN and TBL >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 Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly CP/CRP and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly CP/CRP to allow the inadvertently enrolled subject to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

Subjects will be discontinued in 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)
- The investigator decides that the subject should be discontinued from the study

- The subject, or legal representative, requests to be withdrawn from the study
- If a suicide-related thought or behavior is identified at any time during the study, or if during the study a subject gives:
    - A "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS; or
    - A "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS; or
    - A "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS.

In addition, a subject will also be evaluated for discontinuation if they have self-injurious behavior that would be classified as non-suicidal self-injurious behavior. It is recommended that a subject be assessed by a psychiatrist or appropriately trained professional to assist the investigator in deciding whether the subject should be discontinued 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 study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

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. 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 healthcare 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, study site personnel will record, via electronic CRF (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, study device and/or study procedure and the AE.

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

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

9.1.1. Serious Adverse Events

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

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

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

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

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

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

9.1.1.1. 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.

9.1.2. 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.

9.2. Treatment of Overdose

For the purposes of this study, an overdose of lasmiditan is considered any dose higher than the dose assigned through randomization.

There is no specific antidote for lasmiditan. In the event of overdose, the subject should receive appropriate supportive care and AEs should be documented.

Refer to the IB for further information.

9.3. Safety

9.3.1. Laboratory Tests

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

All safety laboratory tests during the study will be analyzed by a local laboratory.

9.3.2. Vital Signs

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

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

When 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.

9.3.3. 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.

9.3.4. Colombia-Suicide Severity Rating Scale

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. Any occurrence of suicide-related thoughts and behaviors will be assessed as indicated in the Schedule of Activities (Section 2) using the C-SSRS. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience.

Before administering the C-SSRS, study site personnel will question the subject about any change in the preexisting condition(s) and the occurrence and nature of any AEs. If a suicide-related event is discovered during the C-SSRS administration, but was not captured as an AE, the site 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.

The first time the scale is administered in this study, the C-SSRS 'Baseline-Screening' 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 clinically significant finding is identified, 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.

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.

9.3.5. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- adverse events

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

9.3.5.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3 × ULN, ALP ≥2 × ULN, or elevated TBL ≥2 × ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, 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 CP/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 TBL to ≥2 × ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.4. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan and metabolites M7, M8, (S,R)-M18, and (S,S)-M18. A maximum of 3 plasma 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.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.4.1. 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 metabolites M7, M8, (S,R)-M18, and (S,S)-M18 will be assayed using a validated liquid chromatography with tandem mass spectrometry method. Analyses of samples collected from placebo-treated subjects are not planned.

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.

9.5. Pharmacodynamics

Not applicable.

9.6. Genetics

Not applicable.

9.7. Biomarkers

Not applicable.

9.8. Health Economics

Not applicable.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size is customary for Phase 1 studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized but not administered treatment may be replaced to ensure that approximately 8 subjects per cohort, who receive lasmiditan, may 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, and other demographic characteristics will be recorded and summarized using descriptive statistics.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee. Further detail on required analyses will be presented in the statistical analysis plan.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least one dose of the IP and have evaluable PK. Safety analyses will be conducted for all enrolled subjects, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes 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 safety analyses will be performed using the safety population which will consist of subjects who received at least 1 dose of IP.

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 lab parameters and vital signs. The parameters will be listed, and summarized using standard descriptive statistics, as appropriate.

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

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan and metabolites M7, M8, (S,R)-M18, and (S,S)-M18 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be area under the concentration versus time curve (AUC) from zero to infinity (AUC[0-∞]) [single-dose only], AUC over a dosing interval (AUC[0-τ]), maximum observed drug concentration (C_{max}), and time of maximum observed drug concentration (t_{max}). Other noncompartmental parameters, such as half-life, apparent clearance, apparent volume of distribution, and accumulation ratio may be reported.

Trough concentrations of lasmiditan and its metabolites will be evaluated graphically and/or descriptively for achievement of steady-state. No formal analysis will be performed for attainment of steady-state.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters for lasmiditan will be evaluated to estimate dose proportionality over the 50 to 200-mg dose range on Day 1 and Day 10. Log-transformed C_{max} and AUC parameters (AUC[0-∞] for Day 1 and AUC[0-τ] for Day 10) will be evaluated using a power model (where the log of the dose will be an explanatory variable) to estimate ratios of dose-normalized geometric means and the corresponding 90% confidence intervals (CIs). The estimated ratio between the highest and lowest doses will be used to assess dose proportionality. The intersubject coefficient of variation will be derived.

10.3.3. Data Review During the Study

This section is not applicable for this study.

10.3.4. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP/CRP/investigator or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

11. References

None cited.

Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-∞)	area under the concentration versus time curve from zero to infinity
AUC(0-τ)	area under the concentration versus time curve over a dosing interval
blinding	A procedure in which one or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
CI	confidence interval
C_{max}	maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	clinical pharmacologist
CRF/eCRF	case report form/electronic case report form

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
ECG	electrocardiogram
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for 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.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
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.
IP	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.
IWRS	interactive web-response system
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.
PK	pharmacokinetic
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
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[a]

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Calcium
Mean cell hemoglobin	Phosphorus
Mean cell hemoglobin concentration	Magnesium
Leukocytes (WBC)	Glucose (random)
Platelets	Urea
Differential WBC (absolute counts and % of):	Uric acid
Neutrophils	Total cholesterol
Lymphocytes	Total protein
Monocytes	Albumin
Eosinophils	Total bilirubin
	Direct bilirubin[b]
Basophils	Alkaline phosphatase
	Aspartate aminotransferase
Urinalysis	Alanine aminotransferase
Specific gravity	Creatinine
pH	Gamma-glutamyl transferase
Protein	
Glucose	
Ketones	Urine drug screen[c]
Bilirubin	Alcohol testing[c]
Urobilinogen	Hepatitis B surface antigen[d]
Blood	Hepatitis C antibody[d]
Nitrite	Human immunodeficiency virus antibodies[d]
Microscopic examination (reflex if blood or nitrite is positive)	Pregnancy test
	FSH (postmenopausal females only)[d]

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

a All safety laboratory tests will be analyzed at a local laboratory

b Direct bilirubin will be analyzed if total bilirubin is elevated above upper limit of normal

c Performed at screening and admission to Clinical Research Unit only

d Performed at screening only

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.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for subjects. 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 ethical review board (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 investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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

Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor,

applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Red blood cells	Prothrombin time
White blood cells	Prothrombin time, INR
Neutrophils	
Lymphocytes	**Hepatic Serology[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	
Alanine aminotransferase	**Anti-nuclear antibody[a]**
Aspartate aminotransferase	**Alkaline phosphatase isoenzymes[a]**
Gamma-glutamyl transferase	**Anti-smooth muscle antibody (or anti-actin**
Creatine phosphokinase	**antibody)[a]**

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

[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-LAIC Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	21.5	1	21.5
Clinical laboratory tests[a]	7.5	6	45
Pharmacokinetics[b]	2	34	68
Total			134.5
Total for clinical purposes (rounded up to nearest 10 mL)			140

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

[b] A maximum of 3 samples may be collected at additional time points during the study if warranted.

Appendix 6. Protocol Amendment H8H-MC-LAIC(a) Summary Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects

Overview

Protocol H8H-MC-LAIC [Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Chinese Subjects] has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Table LAIC.3. Amendment Summary for Protocol H8H-MC-LAIC Amendment(a)

Section # and Name	Description of Change	Brief Rationale
6.2. Exclusion Criteria	Exclusion criteria 16 has been expanded to include a list of excluded medical history/current medical conditions.	The list has been added to provide clarity to the study site.
7.1.1. Packaging and Labelling	Provision of lasmiditan and placebo tablets has been changed from bulk supply in bottles to a blister.	Change reflects current format of tablet supply.
7.2. Method of Treatment Assignment	The method of randomization has been changed from using a computer generated randomization schedule to a computer-generated random sequence using an interactive web-response system (IWRS)	Change reflects randomization method used by the study site.
7.3 Blinding	The method of unblinding has been changed from emergency codes to being performed through the IWRS.	Change reflects unblinding procedure when using an IWRS.

Revised Protocol Sections

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

6.2. Exclusion Criteria

[16] have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the IP; or of interfering with the interpretation of data. Examples of excluded conditions include, but are not limited to; hypertension, angina, heart failure, asthma (childhood asthma is acceptable), chronic obstructive airways disease, hepatitis, cirrhosis, renal impairment, diabetes, anemia, migraine, fits, seizures (except febrile convulsions), significant head trauma, surgical resection of bowel (appendectomy is acceptable), or any other condition requiring chronic medication

7.1.1. Packaging and Labelling

Each tablet of lasmiditan contains 50 or 100 mg of active ingredient and is provided ~~as bulk supply in bottles~~ in a blister. Placebo tablets look identical but contain no active ingredient and will be provided in a similar ~~bulk bottles~~ blister.

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

7.2 Method of Treatment Assignment

Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The IWRS will be used to assign a blister containing double-blind IP to each subject. ~~Subjects will be randomized to lasmiditan or placebo treatment using a computer-generated allocation schedule.~~

7.3 Blinding

~~Emergency codes will be available to the investigator. A code, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.~~ Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the subject's well-being requires knowledge of the subject's treatment assignment. All unblinding events are recorded and reported by the IWRS.

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