Protocol H8H-JE-LAIE

Safety, Tolerability, and Pharmacokinetics of Lasmiditan in Healthy Japanese and Caucasian Subjects

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Confidential Information

Lasmiditan (LY573144)

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PPD

Clinical Pharmacology Protocol 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 Japanese and Caucasian Subjects

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

This study is the first clinical evaluation of lasmiditan in Japanese subjects, and will facilitate subsequent clinical trials in Japanese patients. Characterization of the safety and pharmacokinetics (PK) of lasmiditan in Japanese subjects is essential for further clinical development in Japan. Additionally, as the majority of migraine patients are female, and previous studies suggest a higher exposure in female subjects, the safety and PK in female Japanese subjects will also be explored. Caucasian subjects are included to explore the relationship of safety, tolerability, and PK of lasmiditan between Japanese and Caucasian subjects.

Objectives/Endpoints:

Objectives	Endpoints
Primary To explore the safety and tolerability of single and repeated oral doses of lasmiditan in healthy Japanese subjects, and single oral doses of lasmiditan in healthy Caucasian subjects.	Incidence of treatment-emergent adverse events and serious adverse events.
Secondary To evaluate the PK of lasmiditan in healthy Japanese and Caucasian subjects	Area under the concentration (AUC) versus time curve from time 0 extrapolated to infinity [AUC(0-∞)], maximum observed plasma concentration (C_{max}), and time of maximum observed plasma concentration (t_{max}).

Summary of Study Design:

This is a randomized, 3-period, subject- and investigator-blind crossover study in healthy Japanese and Caucasian subjects.

Subjects will be enrolled into 1 of 3 cohorts; Japanese subjects will be enrolled into Cohorts 1 and 2, and Caucasian subjects will be enrolled into Cohort 3. Within each cohort, subjects will be randomized to a treatment sequence; there will be 3 treatment sequences in Cohort 1, and 4 treatment sequences in each of Cohorts 2 and 3. Randomization will be stratified by sex, such that there will be an approximately equal number of male and female subjects in each cohort.

Investigational product will be administered after a fast of at least 8 hours. Blood samples for PK analysis will be collected predose and for up to 48 hours postdose in each period. There will be a washout period of approximately

72-hours between dose administrations across periods. Subjects will attend a follow-up visit 7 to 10 days following discharge from the clinical research unit.

Safety and tolerability will be assessed throughout the study by means of adverse event review, physical examinations, body weight, vital sign measurements, electrocardiograms, clinical laboratory tests, and Columbia-Suicide Severity Rating Scale.

Treatment Arms and Planned Duration for an Individual Subject:
Subjects will participate in: a screening period of up to 27 days; 3 treatment periods, each of either 4 days (Period 1) or 3 days (Periods 2 and 3) duration; and a follow-up period of up to 10 days. The total study duration for each subject will be up to 47 days.

Cohorts 1 and 3: Subjects will receive a single dose of 50 mg lasmiditan or placebo in Period 1, 100 mg lasmiditan or placebo in Period 2, and 200 mg lasmiditan or placebo in Period 3.

Cohort 2: Subjects will receive single dose of 50, 100, or 200 mg lasmiditan or placebo in Period 1, 400 mg lasmiditan or placebo in Period 2, and 2 doses of 200 mg lasmiditan or 2 doses of placebo administered 2 hours apart in Period 3.

Number of Subjects:
Up to 16 Japanese and 11 Caucasian subjects may be enrolled and randomized so that approximately 14 Japanese and 8 Caucasian subjects (approximately 2 per treatment sequence) complete the study.

Statistical Analysis:

Safety parameters will be listed and summarized using standard descriptive statistics, where applicable. The relationship between concentrations of lasmiditan and changes from baseline corrected QT interval based on Fridericia's formula (ΔQTcF) will be explored to assess the effect of lasmiditan concentration on the ΔQTcF.

Pharmacokinetic parameters for lasmiditan will be evaluated to determine dose proportionality for Japanese and Caucasian subjects. Log transformed C_{max} and AUC(0-∞) 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. The estimated ratio between the highest and lowest doses for each race (Japanese, Caucasian) will be used to assess dose proportionality.

2. Schedule of Activities

Study Schedule Protocol H8H-JE-LAIE

	Screening	Period 1				Period 2			Period 3			Follow-up/ED	Comments
		Day											
Procedure	-28 to -2 days prior to Day 1 of Period 1	-1	1	2	3	1	2	3	1	2	3	7 to 10 days following Day 3 of Period 3	
Informed Consent	X												
Subject Admission to CRU		X											
Subject Discharge from CRU											X		
Chest X-ray	X												
Enrollment/ Randomization			X										
Lasmiditan Administration			X			X			X[a]				A washout of approximately 72 hours between doses across periods
Medical History	X	X											Interim medical history only on Day -1
Urine Drug Screen	X	X											
Alcohol Test		X											
Height	X												
Body Weight	X	X										X	
Triplicate Vital Signs (supine)	X		-1, -0.5, P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	P, 0.5, 1, 1.5, 2, 2.5, 3, 3.5[b], 4, 4.5[b], 5[b], 6, 8, 12	24, 36	48	X	Time points relative to the time of investigational product administration in each period and shown in hours. For repeated doses, timepoints relative to the first dose. Single vital signs only at follow-up/ED. Time points may be added, if warranted and agreed by Lilly and the investigator
Single Orthostatic Vital Signs	X		-1, P, 1, 2, 3, 4, 6, 8, 12	24, 36	48	P, 1, 2, 3, 4, 6, 8, 12	24, 36	48	P, 1, 2, 3, 4, 6, 8, 12	24, 36	48	X	Time points relative to the time of investigational product administration in each period. For repeated doses, time points relative to the first dose. Time points may be added if warranted and agreed by Lilly and the investigator
Clinical Laboratory Tests	X		P			P			P			X	See Appendix 2, Clinical Laboratory Tests, for details

	Screening	Period 1				Period 2			Period 3			Follow-up/ED	Comments
		Day											
Procedure	-28 to -2 days prior to Day 1 of Period 1	-1	1	2	3	1	2	3	1	2	3	7 to 10 days following Day 3 of Period 3	
Adverse Event Review	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test	X	X										X	Serum pregnancy test for all females
Follicle-stimulating hormone	X												Postmenopausal females only
Physical Examination	X	X			X			X			X	X	Full physical examination performed at screening. At other time points, symptom-directed physical examination only
Triplicate 12-lead Electrocardiogram	X		-1, -0.5, P, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	P, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	P, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	X	Time points relative to the time of investigational product administration in each period. For repeated doses, time points relative to the first dose. Refer to Section 9.4.4. Performed after subject has rested in supine position for ~5 to 10 minutes. On days without dosing, should be performed close to the Day 1 dosing time, when possible. Collected in triplicate except at screening and follow-up/ED
Columbia-Suicide Severity Rating Scale/Self-Harm	X	X									X	X	
Genetic Sample			X										Period 1 only
Blood Sample for Lasmiditan and Metabolites Pharmacokinetics			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12	24, 36	48	P, 0.5, 1, 1.5, 2[c], 2.5, 3, 3.5[b], 4, 4.5[b], 5[b], 6, 8, 12	24, 36	48		Time points relative to the time of investigational product administration in each period. For repeated doses, time points relative to the first dose

Abbreviations: CRU = clinical research unit; ED = early discontinuation; P = predose.

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

[a] Subjects in Period 3 of Cohort 2 will receive 2 doses separated by 2 hours.

[b] Subjects in Period 3 of Cohort 2 only.

[c] For subjects in Period 3 of Cohort 2, pharmacokinetic sample collected prior to second dose.

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 lasmiditan in Japanese subjects, and will facilitate subsequent clinical trials in Japanese patients. Characterization of the safety and pharmacokinetics (PK) of lasmiditan in Japanese subjects is essential for further clinical development in Japan. Additionally, as the majority of migraine patients are female, and previous studies suggest a higher exposure in female subjects, the safety and PK in female Japanese subjects will also be explored. Caucasian subjects are included to explore the differences in safety, tolerability, and PK of lasmiditan between Japanese and Caucasian subjects.

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. The most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) in the two 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 400 mg, 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. In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1.5 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 hours. Lasmiditan PK was approximately dose linear. There was an increase of approximately 20% to 30% in maximum observed plasma concentration (C_{max}) and a 30% increase in area under the concentration versus time curve (AUC) in female subjects in a previous study.

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.

3.3. Benefit/Risk Assessment

Oral doses of lasmiditan up to the highest single 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 01 November 2017. Lasmiditan caused no significant QT prolongation either at 100 or 400 mg, and no clinically significant changes in clinical laboratory data. 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 dosing.

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 LAIE.4.1 shows the objectives and endpoints of the study.

Table LAIE.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary To explore the safety and tolerability of single and repeated oral doses of lasmiditan in healthy Japanese subjects, and single oral doses of lasmiditan in healthy Caucasian subjects.	Incidence of TEAEs and SAEs.
Secondary To evaluate the PK of lasmiditan in healthy Japanese and Caucasian subjects.	AUC(0-∞), C_{max}, and t_{max}.
Exploratory To evaluate the PK of metabolites M7, M8, (S,R)-M18, and (S,S)-M18 in healthy Japanese and Caucasian subjects. To explore the safety, tolerability, and PK of lasmiditan in female subjects compared to male subjects.	AUC(0-∞), C_{max}, and t_{max}.

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time 0 extrapolated to infinity; 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 is a randomized, 3-period, subject- and investigator-blind, crossover study in healthy Japanese and Caucasian subjects.

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 in Period 1 (the day before their first dose of lasmiditan or placebo; Section 2).

Subjects will be enrolled into 1 of 3 cohorts. Within each cohort, subjects will be randomized to a treatment sequence, as indicated in Table LAIE.5.2, Table LAIE.5.3, and Table LAIE.5.4. Randomization will be stratified by sex, such there will be an approximately equal number of male and female subjects in each cohort.

Table LAIE.5.2. Treatment Sequences for Cohort 1; Japanese Subjects

Treatment Sequence	Period 1	Period 2	Period 3
1	Placebo	100 mg lasmiditan	200 mg lasmiditan
2	50 mg lasmiditan	Placebo	200 mg lasmiditan
3	50 mg lasmiditan	100 mg lasmiditan	Placebo

Table LAIE.5.3. Treatment Sequences for Cohort 2; Japanese Subjects

Treatment Sequence	Period 1	Period 2	Period 3[a]
1	Placebo	400 mg lasmiditan	2 × 200 mg lasmiditan
2	50 mg lasmiditan	Placebo	2 × 200 mg lasmiditan
3	100 mg lasmiditan	400 mg lasmiditan	2 × placebo
4	200 mg lasmiditan	400 mg lasmiditan	2 × 200 mg lasmiditan

[a] Doses administered 2 hours apart.

Table LAIE.5.4. Treatment Sequences for Cohort 3; Caucasian Subjects

Treatment Sequence	Period 1	Period 2	Period 3
1	Placebo	100 mg lasmiditan	200 mg lasmiditan
2	50 mg lasmiditan	Placebo	200 mg lasmiditan
3	50 mg lasmiditan	100 mg lasmiditan	Placebo
4	50 mg lasmiditan	100 mg lasmiditan	200 mg lasmiditan

After randomization on Day 1, investigational medical product will be administered orally on the morning of Day 1 after an overnight fast of at least 8 hours. Blood samples will be collected for PK analysis predose, and for up to 48 hours postdose in each period. There will be a washout period of approximately 72 hours between dose administrations across periods.

Subjects will be discharged from the CRU following completion of all scheduled procedures on Day 3 of Period 3, as defined in the Schedule of Activities (Section 2), and will attend a follow-up visit 7 to 10 days following discharge from the CRU on Day 3 of Period 3.

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

Details for the timing of dosing are presented in Section 10.3.3.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Up to 16 Japanese and 11 Caucasian subjects may be enrolled and randomized so that approximately 14 Japanese and 8 Caucasian subjects (approximately 2 subjects per treatment sequence) 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 primary objective of this study, and a crossover design has been chosen to minimize the number of subjects required for the study. The study design that has been chosen is considered to be the most feasible to execute operationally. As this will be the first time that the commercial formulation of lasmiditan will be administered to humans, Caucasian

subjects have been included to allow comparisons between Japanese and Caucasian subjects to be made.

Single and repeated doses (2 single doses administered 2 hours apart) of 50, 100, and 200 mg lasmiditan are considered the planned clinical doses. Additionally, a supratherapeutic dose of 400 mg lasmiditan has been included for the assessment of QT interval. As patients currently receiving approved therapies for migraine may administer an additional dose 2 hours following their initial dose if symptoms do not alleviate, this study will also evaluate the safety, tolerability, and PK of 2 doses of 200 mg lasmiditan administered 2 hours apart.

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 and concomitant medications in patients. Healthy subjects are frequently used in the assessment of bioavailability of both small and large molecules. Conducting this study in Japanese subjects will support their inclusion in future studies with lasmiditan, and inclusion of Caucasian subjects enables the direct comparison between Japanese and Caucasian subjects.

5.5. Justification for Dose

Oral doses of 50, 100, and 200 mg lasmiditan are envisaged to be clinically effective doses, based on data obtained from previous completed studies. A supratherapeutic dose of 400 mg lasmiditan is being investigated to obtain additional PK data and to investigate any effects of lasmiditan on QT interval in Japanese subjects.

6. Study Population

Eligibility of subjects for the study will be based on the results of screening medical history, physical examination, vital sign measurements, ECGs, clinical laboratory tests, chest x-ray, and C-SSRS.

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.

A chest x-ray (posterior anterior and lateral) will be completed at screening unless one has been obtained within the past 12 months, and the x-ray and/or report are available for review.

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 Japanese (first generation) or Caucasian males or females, as determined by medical history and physical examination

CCI

[1a] women of childbearing potential must test negative for pregnancy at screening and on Day -1 of Period 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 lasmiditan.

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.

[1b] 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.

Note: male subjects are not required to adhere to contraceptive requirements.

[2] are aged between 20 and 64 years at screening

[3] have a body mass index 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 or Covance employees

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

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

[12] have previously received the investigational product in this study, withdrawn from this study, or received lasmiditan in any other study investigating lasmiditan

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

[14] have a history of, or ECG findings of, clinically significant bradycardia, heart block, tachycardia, sick sinus syndrome/sinoatrial block, or second or third-degree atrioventricular block, or have any other abnormality in the 12-lead ECG that, in the opinion of the investigator, confounds assessment of QT interval

[15] have an abnormal supine blood pressure (defined as systolic blood pressure <95 or >140 mmHg or diastolic blood pressure <65 or >90 mmHg) at screening. After screening, additional assessments may be performed to confirm eligibility

[16] have a history of syncope, presyncope, uncontrolled vertigo, postural dizziness, or a risk of falls, as judged to be clinically significant by the investigator, or have orthostatic decreases in supine blood pressure of >20 mmHg, or have orthostatic decreases in diastolic blood pressure of >10 mmHg at screening. Measurements of orthostatic blood pressure may be repeated if asymptomatic

[17] have an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 as assessed using the Chronic Kidney Disease Epidemiology Collaboration formula (Section 9.4.1.1)

[18] 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 acceptable

[19] show evidence of significant active neuropsychiatric disease (for example, manic depressive illness, schizophrenia, depression)

[20] have a history of central nervous system conditions such as strokes, transient ischemic attack significant head trauma, central nervous system infections, migraines, brain surgery or any other neurological conditions that, in the opinion of the investigator, increases the risk of participating in the study

[21] currently use or have a history of recreational drug abuse within the past 1 year, show evidence of substance dependence within the past 6 months, or show positive findings on drug screening

[22] show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies

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

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

[25] are women who are pregnant, lactating, or have a positive pregnancy test at screening or admission to the CRU

[26] have used or intend to use over-the-counter or prescription medication including herbal medications within 14 days prior to admission to the CRU and until discharge from the study (with the exception of hormone replacement therapy or occasional acetaminophen use). If minor or inadvertent use of such a product occurs, enrollment of a subject may still be considered appropriate if approved by the investigator and Lilly clinical pharmacologist (CP)/ clinical research physician (CRP; or designee)

[27] have a history of hypersensitivity to any foods or medications, which in the opinion of the investigator, is considered clinically significant

[28] have donated blood of more than 500 mL within 1 month prior to screening

[29] 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 for 48 hours prior to admission to and while resident at the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[30] 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

[31] are unwilling to abide by the dietary or activity restrictions (Section 6.3)

[32] 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 Japanese population for the purposes of this study. The use of lasmiditan in Japanese patients is anticipated, thus this study will specifically examine the PK, safety, and tolerability in Japanese subjects.

Criteria [8] and [9] prevent conflict of interest in study participants. Criteria [10] to [32] 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. Following single doses of lasmiditan, subjects will be fasted for approximately 3 hours postdose. Following repeated doses of lasmiditan, subjects will be fasted for approximately 5 hours following the first dose. 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. Japanese subjects may be provided with meals that are consistent with a typical Japanese diet. When not resident at the CRU, subjects will be encouraged to maintain their normal dietary habit.

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 and while resident at the CRU. At other times during the outpatient period, subjects will be allowed to maintain their regular caffeine consumption.

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 and while resident at the CRU.

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 doses of 50, 100, 200, and 400 mg lasmiditan and repeated doses of 200 mg lasmiditan administered orally, with placebo.

Table LAIE.7.5 and Table LAIE.7.6 show the treatment regimens.

Table LAIE.7.5. Treatments Administered (All periods for Cohorts 1 and 3, Period 1 for Cohort 2)

Treatment Name	LY50	LY100	LY200	PLA
Unit dose, dose level	1 × LY50 + 3 × PLA	2 × LY50 + 2 × PLA	4 × LY50	4 × PLA
Dosing instructions	single oral dose			
Number of tablets administered	4	4	4	4

Abbreviations: LY50 =50 mg lasmiditan, LY100 =100 mg lasmiditan, LY200 =200 mg lasmiditan, PLA=placebo.

Table LAIE.7.6. Treatments Administered (Periods 2 and 3 for Cohort 2)

	Period 2		Period 3	
Treatment Name	LY400	PLA	2 × LY200	PLA
Unit dose, dose level	8 × LY50	8 × PLA	2 doses of 4 × LY50	2 doses of 4 × PLA
Dosing instructions	single oral dose		2 single oral doses separated by 2 hours	
Number of tablets administered	8	8	2 × 4	2 × 4

Abbreviations: LY50 =50 mg lasmiditan, LY200 =200 mg lasmiditan, LY400 =400 mg lasmiditan, PLA=placebo.

Tablets of lasmiditan or placebo will be administered orally with approximately 200 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.

Lasmiditan tablets will be supplemented with the appropriate number of placebo tablets such that each subject receives a total of 4 or 8 tablets in each period (Table LAIE.7.5 and Table LAIE.7.6).

The investigator or designee is responsible for:

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

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

7.1.1. Packaging and Labeling

The 50 mg lasmiditan tablets will be provided in bulk bottles. Placebo-to-match tablets are of identical appearance to 50 mg lasmiditan tablets and will be provided in bulk bottles, but contain no active ingredient.

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

7.2. Method of Treatment Assignment

Japanese subjects will be enrolled in Cohort 1 or 2, and Caucasian subjects will be enrolled into Cohort 3.

Within each cohort, subjects will be randomized to a treatment sequence using a computer-generated allocation schedule. There will be no randomization between cohorts. Randomization will be stratified by sex, such that there will be an approximately equal number of male and female subjects in each cohort.

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 electronic case report form (eCRF).

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 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.

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 CP or 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 the sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

Hormonal contraception and hormone replacement therapy are permitted.

In general, concomitant medication should be avoided; however, acetaminophen (maximum 2 g/24 hours) may be administered at the discretion of the investigator for treatment of headaches etc. 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 AE and other early discontinuation procedures per Section 2 of this protocol.

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

8.1. Discontinuation from Study Treatment

Discontinuation of lasmiditan in subjects with 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 >1.5
- ALT or AST >3 × ULN 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 investigational product.

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice.

- The investigator decides that the subject should be discontinued from the study.
- The subject requests to be withdrawn from the study.

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she 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 (including tolerance limits for timing).

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

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

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

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product, 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 investigational product is discontinued as a result of an AE, study site 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 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 CP/CRP, 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 investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure, then it MUST be reported.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to investigational product or procedure. Lilly

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

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

9.4. 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).

9.4.1.1. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate will be assessed at screening based on estimated creatinine clearance, using the Chronic Kidney Disease Epidemiology Collaboration formula.

$$\text{eGFR} = 141 \times min\left(\frac{SCr}{k,1}\right)^{a} \times max\left(\frac{SCr}{k,1}\right)^{-1.209} \times 0.993^{age} (\times 1.018 \text{ if female})$$

Where: a = -0.329 for females and -0.411 for males; k = 0.7 for females and 0.9 for males; SCr = serum creatinine (mg/dL); max = maximum of SCr/k *or* 1; and min = minimum of SCr/k *or* 1.

9.4.2. Vital Signs

For each subject, vital signs (including orthostatic vital signs) measurements should be conducted according to the Schedule of Activities (Section 2). Supine vital signs should be measured in triplicate; orthostatic vital signs should be measured singly.

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

For orthostatic measurements, 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. Body Weight

For each subject, measurements of body weight will be conducted according to the Schedule of Activities (Section 2).

9.4.4. Electrocardiograms

For each subject, ECGs should be collected according to the Schedule of Activities.

For each subject, a 12-lead digital ECG will be collected in triplicate (single at screening) according to the Schedule of Activities (Section 2). 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. Consecutive replicate ECGs will be obtained at approximately one minute intervals. Electrocardiograms may be obtained at additional times, when deemed clinically necessary.

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

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

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

9.4.5. Columbia-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 pre-existing 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.

9.4.6. Safety Monitoring

The Lilly CP or 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/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.

9.4.6.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3 × ULN, ALP ≥2 × ULN, or elevated total bilirubin ≥2 × ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, 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 a SAE.

9.5. Pharmacokinetics

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

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

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

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities, where local regulations allow.

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

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

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or institutional review board 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

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 14 Japanese and 8 Caucasian subjects (approximately 2 per treatment sequence) 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, body mass index, and other demographic characteristics will be recorded and summarized using descriptive statistics overall and by race.

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 one dose of the investigational product 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.

Where applicable, safety and PK data will be presented separately for Japanese and Caucasian subjects.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, along with the date and time of their occurrence (where available).

If the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment (immediately prior to dose administration on Day 1 of Period 1) will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

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

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include body weight, vital sign measurements, ECG parameters, clinical laboratory tests, 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.

Prior to any statistical analysis of QT interval, QT values will be corrected for heart rate (corrected QT interval based on Fridericia's formula [QTcF]). The relationship between concentrations of lasmiditan and changes from baseline QTcF (ΔQTcF) will be explored to assess the effect of lasmiditan concentration on the ΔQTcF. A detailed analysis for QT interval will be provided in the statistical analysis plan. 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 parameters 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 time of maximum observed plasma concentration (t_{max}), C_{max}, and AUC of lasmiditan and metabolites M7, M8, (S,R)-M18, and (S,S)-M18. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters for lasmiditan will be evaluated to determine dose proportionality for Japanese (Cohorts 1 and 2 over the 50 to 400 mg dose range, excluding any data from Period 3 in Cohort 2) and Caucasian subjects (Cohort 3, over the 50 to 200 mg dose range). Log-transformed C_{max} and AUC from time 0 extrapolated to infinity [AUC(0-∞)] 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. The estimated ratio between the highest and lowest doses for each race (Japanese, Caucasian) will be used to assess dose proportionality. The intersubject coefficient of variation will be derived, and the intrasubject coefficient of variation may also be derived.

Data for Japanese and Caucasian subjects may be pooled if required, and data for male and female subjects may be presented separately to explore the effect of sex.

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

10.3.3. Data Review During the Study

All available safety and tolerability data obtained up to Day 1 of Period 3 of Cohort 1 and Period 1 of Cohort 2 will be reviewed by the investigator prior to dosing in Period 2 of Cohort 2; i.e., dosing in Period 1 of Cohort 2 can commence prior to dosing in Period 3 of Cohort 1.

Dosing of subjects in Cohort 3 can commence irrespective of dosing of subjects in Cohorts 1 and 2.

Safety and PK data may be reviewed throughout the study to support the next study of lasmiditan in Japanese subjects.

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

Not applicable.

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 time 0 extrapolated to infinity
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.
C_{max}	maximum observed plasma 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 requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRU	clinical research unit
C-SSRS	Columbia-Suicide Severity Rating Scale

ΔQTcF	changes from baseline corrected QT interval based on Fridericia's formula
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
eGFR	estimated glomerular filtration rate
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.
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Ig	immunoglobulin
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board
randomize	the process of assigning subjects to an experimental group on a random basis
PK	pharmacokinetic
PLA	placebo
QTcF	corrected QT interval based on Fridericia's formula

SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
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 plasma concentration
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count	Chloride
Mean cell volume	Calcium
Mean cell hemoglobin	Phosphorus
Mean cell hemoglobin concentration	Glucose (random)
Leukocytes (WBC)	Blood urea nitrogen
Platelets	Uric acid
Differential WBC (Absolute counts of):	Total cholesterol
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Alkaline phosphatase
Basophils	Aspartate aminotransferase
	Alanine aminotransferase
Urinalysis	Creatinine
Specific gravity	Gamma-glutamyl transferase
pH	Estimated glomerular filtration rate[a,b]
Protein	
Glucose	
Ketones	Alcohol testing[c]
Bilirubin	Urine drug screen[d,e]
Urobilinogen	Hepatitis B surface antigen[a]
Blood	Hepatitis C antibody[a]
Nitrite	Human immunodeficiency virus antibodies[a]
Leukocyte-esterase	Pregnancy test[f]
Color and appearance	Follicle-stimulating hormone[a,f]

Abbreviations: WBC = white blood cells.

a Performed at screening only.

b Calculated using Chronic Kidney Disease Epidemiology Collaboration formula (Section 9.4.1.1).

c Performed at check-in only.

d Performed at screening and check-in.

e Includes amphetamines/methamphetamines, barbiturates, benzodiazepines, cocaine (metabolite), methadone, phencyclidine, opiates, and tetrahydrocannabinol/cannabinoids.

f Females 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. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant 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 institutional review board (IRB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

The study site's IRB should be provided with the following:

- the current Investigator's Brochure and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

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

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

Protocol Signatures

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

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

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

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the electronic case report forms, 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 electronic case report form 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 IRBs 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 IRB 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 clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
Red blood cells	Prothrombin Time
White blood cells	Prothrombin Time, International Normalized Ratio
Neutrophils	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
Alanine aminotransferase	**Anti-nuclear antibody[a]**
Aspartate aminotransferase	**Alkaline Phosphatase Isoenzymes[a]**
Gamma-glutamyl transferase	**Anti-smooth muscle antibody (or anti-actin antibody)[a]**
Creatine kinase	

Abbreviation: Ig = immunoglobulin.

[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. The table below is representative of the cohort for which the highest volume of blood will be drawn.

Protocol H8H-JE-LAIE Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	19.5	1	19.5
Clinical laboratory tests[a]	12.5	4	50
Pregnancy tests	3.5	2	7
Pharmacokinetics[b]	2	45	90
Pharmacogenetics	10	1	10
Total			176.5
Total for clinical purposes			180

[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.

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