Protocol H8H-MC-LAIA

Bioequivalence of Lasmiditan Oral Disintegrating Tablet Compared to Current Immediate-Release Tablet Formulation to Support Treatment of Migraine

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Approval Date: 8-Sep-2020

Title Page

Protocol Title: Bioequivalence of Lasmiditan Oral Disintegrating Tablet Compared to Current Immediate-Release Tablet Formulation to Support Treatment of Migraine

Protocol Number: H8H-MC-LAIA

Amendment Number: This is the initial protocol

Compound: Lasmiditan (LY573144)

Study Phase: 1

Short Title: Bioequivalence of lasmiditan oral disintegrating tablet compared to current immediate-release tablet formulation to support treatment of migraine

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

IND: 103420

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 08-Sep-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Bioequivalence of Lasmiditan Oral Disintegrating Tablet Compared to Current Immediate-Release Tablet Formulation to Support Treatment of Migraine

Short Title: Bioequivalence of lasmiditan oral disintegrating tablet compared to current immediate-release tablet formulation to support treatment of migraine.

Rationale: Previous clinical studies of lasmiditan have used an immediate-release (IR) tablet formulation. An oral-disintegrating (OD) tablet has been developed to aid pediatric development and for more convenient administration in adults, e.g., for those who have difficulty swallowing a tablet. This study is intended to determine the bioequivalence, safety, and tolerability of a newly developed OD tablet of lasmiditan compared to the current IR tablet.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the PK of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) administered without water versus the current IR tablet formulation (reference) in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To evaluate the PK of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) administered with water versus the current IR tablet formulation (reference) in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
• To evaluate the safety and tolerability of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) versus the current IR tablet formulation (reference) in healthy participants	• Incidence of TEAEs and SAEs

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t_{last}) = area under the concentration time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; IR = immediate release; OD = oral disintegrating; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Overall Design

Screening

All participants will be screened within 28 days prior to enrollment.

Treatment and Assessment Period

Eligible participants will take part in 3 separate dosing periods. In each period, participants will be admitted to the clinical research unit (CRU) on Day -1 and remain resident in the CRU until discharge on Day 6.

There will be a washout period of ≥5 days between the day of dosing in 1 period and the day of dosing in the subsequent period. Days 5 and 6 of Period 1 and 2 may coincide with Days -1 and 1 of Period 2 and 3, respectively, provided the required washout between lasmiditan doses is observed.

On Day 1 of Period 1, participants will be equally randomized to receive a 100-mg oral dose in 1 of 6 dosing sequences in each of 3 dosing periods.

Pharmacokinetic blood sampling and safety assessments, including vital sign measurements, physical examinations, clinical laboratory tests, electrocardiograms, and adverse event recording will be performed according to the Schedule of Activities.

Follow-up

Day 6 of Period 3 will be considered the final visit of the study.

Disclosure Statement: This is a Phase 1, open-label, randomized, single-dose, 3-way crossover study, with 6 sequences in healthy participants.

Number of Participants: Approximately 48 participants will be enrolled to ensure that 36 participants, 6 per treatment sequence, complete the study.

Intervention Groups and Duration: Participants will receive single 100-mg doses of lasmiditan in each of 3 dosing periods, according to 1 of the randomized sequences detailed below.

Dosing Sequences for Protocol H8H-MC-LAIA

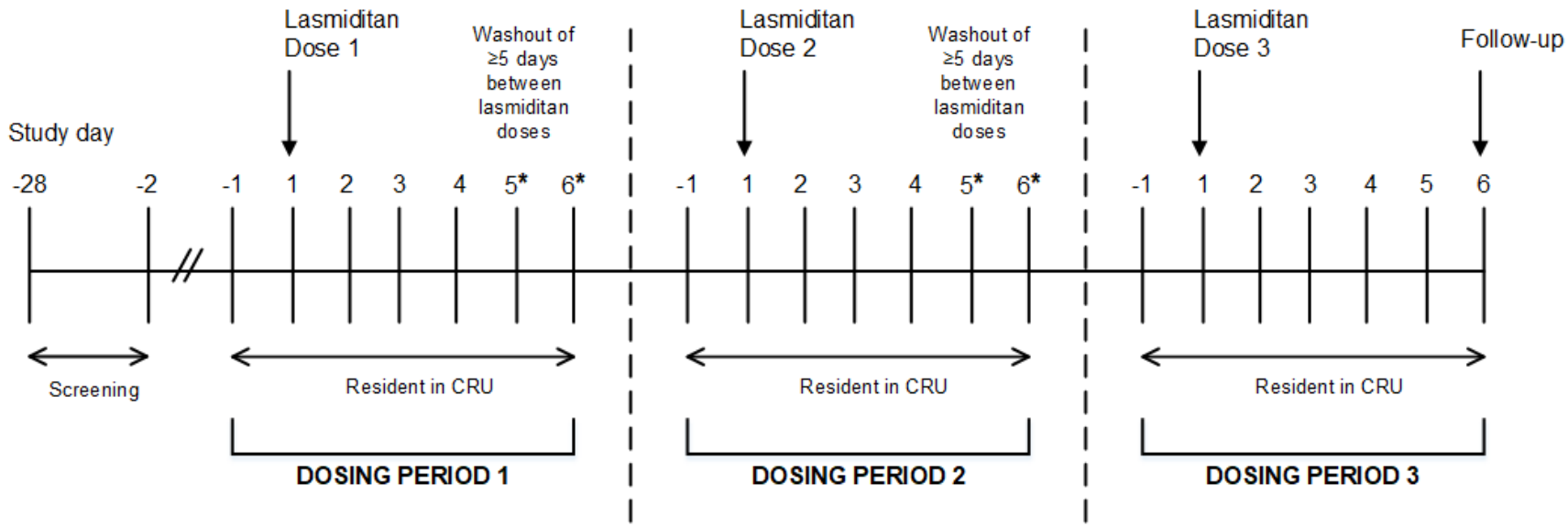
Sequence	Period 1	Period 2	Period 3
1	IR (reference)	OD without water (test)	OD with water (test)
2	IR (reference)	OD with water (test)	OD without water (test)
3	OD without water (test)	OD with water (test)	IR (reference)
4	OD without water (test)	IR (reference)	OD with water (test)
5	OD with water (test)	IR (reference)	OD without water (test)
6	OD with water (test)	OD without water (test)	IR (reference)

Abbreviations: IR = immediate release; OD = oral disintegrating.

Screening will occur up to 28 days prior to enrollment. Each participant will take part in 3 treatment periods. In each period, participants will be admitted to the CRU on Day -1 and remain resident in the CRU until discharge on Day 6. At the discretion of the investigator, participants may remain resident in the CRU for the entirety of the study, i.e., from admission to the CRU on Day -1 of Period 1 until discharge from the CRU on Day 6 of Period 3, after all assessments have been completed.

Data Monitoring Committee: No

1.2. Schema



* Days 5 and 6 may be equivalent to Days -1 and 1, respectively, for the next treatment period if a minimum of 5 days between lasmiditan doses is observed

1.3. Schedule of Activities (SoA)

Study Schedule Protocol H8H-MC-LAIA

	Screening	Dosing Periods 1 to 3								Comments
Procedure	-28 to -2 days prior to D1	D-1[a]	D1[a]	D2	D3	D4	D5[a]	D6[a]	ED	
Informed consent	X									
Admission to CRU		X								Participants may remain at the CRU throughout the duration of the study, at the discretion of the investigator, i.e., admission to CRU in Period 1 only.
Discharge from CRU								X		Participants may remain at the CRU throughout the duration of the study, at the discretion of the investigator, i.e., discharge from CRU in Period 3 only.
Medical history and demographics	X									
Participant eligibility	X									Confirm participant eligibility against inclusion and exclusion criteria (see Section 5).
Lasmiditan administration			X							A minimum washout of 5 days between lasmiditan doses is required.
Height	X									
Weight	X									
Urine drug screen	X	X								On D-1, only required if participant is being admitted to CRU.
Alcohol breath test	X	X								On D-1, only required if participant is being admitted to CRU.
Pregnancy test	X	X								Serum pregnancy test to be performed at screening. Urine pregnancy test to be performed on D-1 (admission to CRU only).
Supine vital signs (pulse rate, blood pressure, and oral body temperature)	X	X	P, 1, 2 h	24 h					X	Time points may be added for each period, if warranted and agreed up on between Lilly and the investigator.
12-lead ECG	X		P							

	Screening	Dosing Periods 1 to 3								Comments
Procedure	-28 to -2 days prior to D1	D-1[a]	D1[a]	D2	D3	D4	D5[a]	D6[a]	ED	
Clinical laboratory tests	X	X		24 h					X	See Appendix 2 (Section 10.2) for details.
Full physical examination	X									Additional symptom-driven physical examinations may be performed at the discretion of the investigator.
Pharmacogenetic blood sample			P							D1 of Period 1 only.
PK sampling in plasma (lasmiditan and M8)			P, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 h	24 h	48 h	72 h	96 h	120 h		The 120 h sample may serve as the D1 predose sample for subsequent periods, if participants are remaining in-house.
Product acceptability and palatability			X							D1 of dosing periods when the OD tablet is administered either with or without water. Complete questionnaire immediately after OD tablet administration.
Adverse event review	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; D = Day; ED = early discontinuation; h = hour; M8 = metabolite 8; OD = oral disintegrating; P = predose; PK = pharmacokinetic(s).

[a] The Day 5 and Day 6 visits of a treatment period may occur at the same time as the Day -1 and Day 1 visits, respectively, of the subsequent treatment period. Therefore, assessments that occur on both visits will only be performed once. All results must be reviewed prior to dosing on Day 1 of each treatment period. The Day 6 visit of Treatment Period 3 will be considered the final visit.

2. Introduction

Lasmiditan (LY573144) has been developed by Eli Lilly and Company (Lilly), and approved by the Food and Drug Administration (FDA), for the acute treatment of migraine with or without aura in adults. Full details of the preclinical and clinical safety and tolerability data are contained in the Investigator's Brochure (IB).

2.1. Study Rationale

Previous clinical studies of lasmiditan have used an immediate-release (IR) tablet formulation. An oral-disintegrating (OD) tablet has been developed to support pediatric development and for more convenient administration in adults, e.g., for those who have difficulty swallowing a tablet.

This study is intended to determine the bioequivalence, safety, and tolerability of a newly developed OD tablet of lasmiditan compared to the current IR tablet. Information on the acceptability and palatability of the OD tablet will also be collected during the study.

2.2. Background

Lasmiditan is a low-molecular-weight agonist of the 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor with a nonvascular and primarily neural mechanism of action. It has a high affinity for the human 5-HT_{1F} receptor and a >440-fold selectivity for the human 5-HT_{1F} receptor relative to the 5-HT_{1B} receptor. Lasmiditan has high solubility and permeability.

Lasmiditan doses have been evaluated in healthy participants or patients with migraine across completed Phase 1, 2, and 3 clinical studies. Across these studies, single intravenous and single oral doses of lasmiditan were administered over a range of 0.1 mg to 400 mg. Multiple oral doses of 200 mg or 400 mg were administered orally once daily (QD) for 7 days. Cumulatively through 14 August 2018, approximately 4945 participants have received lasmiditan. The most frequently reported lasmiditan adverse events (AEs) 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, and nausea, and the majority were mild or moderate in severity. Safety and tolerability in healthy participants were similar up to the highest dose of 400 mg administered as a single and multiple (QD for 7 days) dose, with drowsiness, dizziness, and paresthesia being the most frequently reported AEs. The majority of these were mild in severity, and none were severe.

In previous studies, following single oral dose administration of lasmiditan to healthy participants, lasmiditan was absorbed with a median time of maximum observed drug concentration (t_{max}) of 1.8 hours, and rapidly eliminated with a mean terminal half-life ($t_{1/2}$) of approximately 5.7 hours. Lasmiditan exposure increased in a dose-dependent manner that was considered to be approximately linear with dose over a clinical dose range of 50 to 200 mg. No accumulation of lasmiditan was previously observed with repeated QD dosing of 200 or 400 mg. Lasmiditan undergoes extensive hepatic and extrahepatic metabolism with ketone reduction to inactive metabolite 8 (M8) as the major biotransformation pathway.

2.3. Benefit/Risk Assessment

There is no anticipated therapeutic benefit for the healthy participants.

A 100-mg dose of lasmiditan will be used in the current study. Oral doses of lasmiditan up to the highest single and multiple oral dose given (400 mg) were well tolerated in healthy participants, with no drug-related serious adverse events (SAEs) or withdrawals due to AEs as of 14 August 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 a mean decrease in heart rate of 5 to 10 bpm compared to 2 to 5 bpm for placebo. Additionally, in non-elderly healthy volunteers, a mean increase in blood pressure of approximately 2 to 3 mmHg was observed 1 hour after dosing with 200 mg lasmiditan. There were no additional findings on vital signs following QD dosing for 7 days. Overall, in previous healthy volunteer studies, these changes were well tolerated. Although central nervous system disorders were commonly reported as AEs, especially at higher dose levels, they were generally mild or moderate in intensity.

Participants should avoid driving or operating machinery for at least 8 hours following dosing with lasmiditan. This risk is mitigated in the current study as participants will be confined to the clinical research unit (CRU).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of lasmiditan may be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the PK of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) administered without water versus the current IR tablet formulation (reference) in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
Secondary	
• To evaluate the PK of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) administered with water versus the current IR tablet formulation (reference) in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
• To evaluate the safety and tolerability of lasmiditan following administration of a single 100-mg dose of lasmiditan OD tablet (test) versus the current IR tablet formulation (reference) in healthy participants	• Incidence of TEAEs and SAEs
Exploratory	
• To characterize the PK of M8 following administration of a single 100-mg dose of lasmiditan OD tablet (test) or the current IR tablet formulation (reference) in healthy participants	• C_{max}, AUC(0-∞), and AUC(0-t_{last})
• To assess the product acceptability and palatability of lasmiditan OD tablets	• Responses to OD tablet acceptability and palatability questionnaire

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-t_{last}) = area under the concentration time curve from time zero to time t, where t is the last time point with a measurable concentration; C_{max} = maximum observed drug concentration; IR = immediate release; M8 = metabolite 8; OD = oral disintegrating; PK = pharmacokinetics; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study H8H-MC-LAIA (LAIA) is a Phase 1, open-label, randomized, single-dose, 3-way crossover study in healthy participants. Approximately 48 participants will be enrolled such that 36 participants, 6 per treatment sequence, complete the study.

Screening

All participants will be screened within 28 days prior to enrollment.

Treatment and Assessment Period

Eligible participants will take part in 3 separate dosing periods. In each period, participants will be admitted to the CRU on Day -1 and remain resident in the CRU until discharge on Day 6. At the discretion of the investigator, participants may remain resident in the CRU for the entirety of the study, i.e., from admission to the CRU on Day -1 of Period 1 until discharge from the CRU on Day 6 of Period 3, after all assessments have been completed.

There will be a washout period of ≥5 days between the day of dosing in 1 period and the day of dosing in the subsequent period. Days 5 and 6 of Period 1 and 2 may coincide with Days -1 and 1 of Period 2 and 3, respectively, provided the required washout between lasmiditan doses is observed.

On Day 1 of Period 1, participants will be equally randomized to receive a 100-mg oral dose in 1 of 6 dosing sequences in each of 3 dosing periods as shown in Table LAIA.1.

Table LAIA.1. Dosing Sequences for Protocol H8H-MC-LAIA

Sequence	Period 1	Period 2	Period 3
1	IR (reference)	OD without water (test)	OD with water (test)
2	IR (reference)	OD with water (test)	OD without water (test)
3	OD without water (test)	OD with water (test)	IR (reference)
4	OD without water (test)	IR (reference)	OD with water (test)
5	OD with water (test)	IR (reference)	OD without water (test)
6	OD with water (test)	OD without water (test)	IR (reference)

Abbreviations: IR = immediate release; OD = oral disintegrating.

Pharmacokinetic blood sampling and safety assessments, including vital sign measurements, physical examinations, clinical laboratory tests, electrocardiograms (ECGs), and AE recording will be performed according to the SoA (Section 1.3).

Follow-up

Day 6 of Period 3 will be considered the final visit of the study.

4.2. Scientific Rationale for Study Design

In order to minimize any potential period effect and to allow each participant to act as his/her own control, a randomized, 3-sequence, crossover design has been selected.

Based on the $t_{1/2}$ of lasmiditan and its metabolites, at least 5 days between the day of dosing in 1 period and the day of dosing in the subsequent period is considered sufficient time for the study drug to washout.

Conducting the study in healthy participants mitigates the potential confounding effects of the disease state and concomitant medications in participants with migraine. A population of healthy participants is frequently used in the assessment of the pharmacokinetics (PK) of both small and large molecules.

This study will be open label as the study primary endpoint PK measures are objective rather than subjective.

4.3. Justification for Dose

An oral dose of 100 mg lasmiditan is a clinically effective dose for the target population, based on data obtained from previous completed studies.

Previous studies in healthy participants have shown single doses of lasmiditan up to 400 mg are generally safe and well tolerated.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

Eligibility of participants for enrollment in 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.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only and at the discretion of the investigator through predose Day 1 (Period 1 only) for safety, not continuously throughout the trial.

Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, repeat the following screening tests and procedures: weight, vital signs, ECG, clinical laboratory tests, and pregnancy test (females only).

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Participant Characteristics

1. Are males or females from 18 to 65 years of age inclusive, at the time of signing the informed consent.
   For contraception requirements of this protocol, see Appendix 4 (Section 10.4).
2. Have a body mass index of 19.0 to 35.0 kg/m^2, inclusive at the time of screening.
3. Are overtly healthy as determined by medical evaluation including:
   - medical history
   - physical examination
   - laboratory tests
   - ECG
   - vital signs.
4. Have clinical laboratory test results within normal reference range for the population or CRU, or results within 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.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Have known allergies to lasmiditan, related compounds, or any components of the formulation of lasmiditan, or a history of significant atopy.
2. Have a history of clinically significant allergic reactions to medications or food products, at the discretion of the investigator.
3. Have an abnormal blood pressure and/or pulse rate, as determined by the investigator.
4. Have clinically significant abnormalities on ECG, as determined by investigator.
5. Have a history or presence of cardiovascular, respiratory, 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 interventions; or of interfering with the interpretation of data.
   Note: Uncomplicated procedures such as appendectomy, splenectomy, and cholecystectomy are considered as acceptable, at the discretion of the investigator.
6. Show a history of central nervous system conditions such as strokes, transient ischemic attacks, significant head trauma, seizures, central nervous system infections, migraine, brain surgery, or any other neurological conditions that, in the opinion of the investigator, increase the risk of participating in the study.
7. Have a history or presence of neuropsychiatric disease (e.g., manic depressive illness, schizophrenia, depression) considered as clinically significant by the investigator.

Prior/Concomitant Therapy

8. Have used or are intending to use over-the-counter or prescription medication, including dietary supplements, within 14 days prior to dosing and until study discharge (apart from occasional acetaminophen, hormonal contraception, or hormone-replacement therapy).

Prior/Concurrent Clinical Study Experience

9. Are currently enrolled in any other clinical study involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study.
10. Have participated, within the past 30 days of admission, in a clinical study involving any study intervention. If the previous study intervention has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.
11. Have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received the investigational product.

Diagnostic assessments

12. Have positive findings on drug screening.
13. Show evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies.
14. Show evidence of hepatitis B and/or have a positive hepatitis B surface antigen test result at screening.

15. Show evidence of hepatitis C and/or have positive hepatitis C antibody test result at screening.
    Note: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
16. Positive hepatitis C RNA test result at screening.
    Note: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

Other Exclusions

17. Have donated blood of more than 500 mL within the previous 2 months of screening.
18. Regularly use known drugs of abuse or have a past history of drug abuse.
19. 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 from 24 hours prior to admission and whilst resident at the CRU. At all other times, participants must agree to consume no more than 3 units per day (males) and 2 units per day (females). (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).
20. Smoke more than 10 cigarettes or e-cigarettes, or 3 cigars, or 3 pipes, per day and are unable to refrain from smoking while resident in the CRU, including the use of any nicotine-containing products (e.g., nicotine patches).
21. Consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day, or are unwilling to stop caffeine consumption 24 hours prior to admission and whilst resident at the CRU. Excessive amount is defined as greater than 6 servings per day (1 serving is approximately equivalent to 120 mg of caffeine).
22. Are unable to comply with the dietary regimen of the CRU.
23. Are females who have a positive pregnancy test at screening or on admission to CRU (Day -1).
24. Are females planning to become pregnant during the study or within 1 month of study completion.
25. Are females who are lactating.
26. Are investigative site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
27. Are Lilly or Covance employees.
28. In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

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

5.3.1. Meals and Dietary Restrictions

During each confinement period, participants will consume only food and beverages that are provided to them by the CRU staff. Standard meals (e.g., breakfast, lunch, dinner, and snack) will be provided to the participants while resident at the CRU.

Lasmiditan will be administered after an overnight fast of at least 8 hours. On Day 1 of each dosing period, participants will abstain from water at least 1 hour before and after dosing (except for water given with the dose). Participants will remain fasting for approximately 4 hours postdose, at which time a meal will be served.

5.3.2. Caffeine, Alcohol, and Tobacco

Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours prior to admission and whist resident in the CRU.

Participants will abstain from alcohol consumption 24 hours prior to admission and while resident at the CRU. At all other times, participants must agree to consume no more than 3 units per day for males or 2 units per day for females.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the CRU.

5.3.3. Activity

Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Repeating of laboratory tests during the screening period or repeating screening assessments to comply with the protocol-designated screening period does not constitute rescreening.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Interventions Administered

This study involves the comparison of a single 100-mg dose of lasmiditan OD tablet (test) versus the current IR tablet formulation (reference). Table LAIA.2 shows the study interventions to be administered.

Table LAIA.2. Study Interventions Administered

Study intervention	Lasmiditan	Lasmiditan
Dosage formulation	Immediate-Release Tablet	Oral-Disintegrating Tablet
Unit dose strength/dosage level	100-mg tablet	100-mg tablet
Route of administration	Oral	Oral
Use	Reference	Test
Dosing instructions	1 tablet taken on Day 1 of the treatment period according to the randomized dosing sequence	1 tablet taken on Day 1 of the treatment period with or without water according to the randomized dosing sequence
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	Study intervention will be provided in a blister. Each blister will be labeled per country requirement	Study intervention will be provided in a blister. Each blister will be labeled per country requirement

6.1.1. Administration Details

Participants will be equally randomized to 1 of 6 dosing sequences in each of 3 dosing periods as described in Section 4.1.

For each dosing period, participants will receive a single oral dose on the morning of Day 1.

- **IR tablet:** Participants receiving the IR tablet formulation will swallow the tablet with 240 mL of room-temperature water.
- **OD tablet (without water):** Immediately before dose administration participants receiving the OD tablet formulation without water will receive 20 mL of room-temperature water to wet their palettes. Then using a dry hand, participants will place the OD tablet on top of the tongue and keep it there until it disintegrates. A gentle pressure may be exerted on the tablet by pressing the tongue against the roof of the mouth to facilitate disintegration of the tablet. The participants will then fully swallow the saliva containing both disintegrated and any un-disintegrated remaining part of the tablet.
- **OD tablet (with water):** Immediately before dose administration participants receiving the OD tablet formulation with water will receive 20 mL of room-temperature water to wet their palettes. Then using a dry hand, participants will place the OD tablet on top of the tongue and keep it there until it disintegrates. A gentle pressure may be exerted on the

tablet by pressing the tongue against the roof of the mouth to facilitate disintegration of the tablet. Once the tablet has disintegrated, the participants will then drink 240 mL of room-temperature water and swallow with the saliva containing both disintegrated and any un-disintegrated remaining part of the tablet.

All doses will be administered in a sitting position and participants will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, 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.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. The investigator or designee will return all unused study interventions to Lilly or its designee at the end of the study. In some cases, sites may destroy the material if, during the CRU selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study; potential bias will be reduced by central randomization.

On Day 1 of Treatment Period 1, participants will be assigned a unique number (randomization number). The randomization number encodes the participant's assignment to 1 of 6 treatment sequences, according to the randomization schedule generated prior to the study by the Statistics Department at Covance. Each participant will be dispensed study intervention, labeled with his/her unique randomization number, throughout the study.

6.4. Study Intervention Compliance

Participants are dosed at the site and they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the electronic case report form (eCRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Concomitant Therapy

Participants must abstain from taking prescription or nonprescription drugs (including dietary supplements) within 14 days prior to dosing and until study discharge, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Acetaminophen, at doses of ≤3 g/24 hours, is permitted for use at the discretion of the investigator for the treatment of headache etc. Contraceptive medication is permitted as per the contraception requirements (Section 10.4) and hormone-replacement therapy is also allowed.

Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Lilly clinical pharmacologist (CP)/clinical research physician (CRP), or designee.

6.6. Dose Modification

Dose modification is not permitted in this study.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Participants discontinuing from study intervention prematurely for any reason should complete AE and other follow-up/early discontinuation procedures as per the SoA (Section 1.3).

Participants discontinuing from the study prematurely for any reason must complete AE and follow-up/early discontinuation procedures as per the SoA (Section 1.3).

Discontinuation of specific sites or of the study as a whole is described in Appendix 1 (Section 10.1.7).

7.1. Discontinuation of Study Intervention

Discontinuation of the study drug for abnormal liver tests **should be considered** by the investigator when a participant 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 and the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if 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.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow-up is as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

A participant 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 participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timings are summarized in the SoA (Section 1.3).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Appendix 2 (Section 10.2) lists the laboratory tests that will be performed for this study.

Appendix 2 (Section 10.2.1) 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.

Assessment collection time

The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF. Failure or being late (that is, outside stipulated time allowances) to perform procedures or obtain samples within the stipulated time allowances due to legitimate clinical issues (for example, equipment technical problems, venous access difficulty) will not be considered protocol deviations. However, the CRU is required to notify the sponsor in writing using a file note.

8.1. Efficacy Assessments

Efficacy is not evaluated in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous illnesses.

Additional symptom-driven physical examinations may be performed at the discretion of the investigator.

Any clinically significant findings in a physical examination should be reported as AEs.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

Blood pressure and pulse rate should be measured after at least 5 minutes supine. For each individual participant, the same cuff size should be used throughout the study for the measurements of blood pressure. The cuff should be attached to the participant's dominant arm.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Where orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 2 minutes, but no longer than 3 minutes. If the participant feels unable to stand, supine vital signs only will be collected.

Additional vital signs may be measured during each dosing period if warranted and agreed upon between Lilly and the investigator.

8.2.3. Electrocardiograms

For each participant, a single 12-lead digital ECG will be collected as outlined in the SoA (Section 1.3).

Electrocardiograms must be recorded before collecting any blood samples. Participants 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 participant is still present, to determine whether the participant meets entry criteria at the relevant visits and for immediate participant management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT/corrected QT interval from baseline) after enrollment, the investigator will determine if the participant can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in participant 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.

8.2.4. Clinical Safety Laboratory Assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The laboratory reports must be filed with the source documents.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly CP.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE), then the results must be recorded in the eCRF.

8.2.5. Safety Monitoring

The Lilly CP or CRP will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures (Section 8.3.1). The Lilly CP or CRP will periodically review:

- trends in safety data
- laboratory analytes
- AEs.

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

8.2.5.1. Hepatic Safety

Close hepatic monitoring

Laboratory tests (Appendix 6, Section 10.6), including ALT, AST, alkaline phosphatase (ALP), and TBL, should be repeated, with the addition of direct bilirubin, gamma-glutamyl transferase, and creatine kinase, within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN
ALP <1.5 × ULN	ALP ≥2 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline

TBL ≥1.5 × ULN	TBL ≥2 × baseline (except for participants with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated CP. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5 × ULN	ALT or AST ≥3 × ULN with hepatic signs/symptoms*, or ALT or AST ≥5 × ULN
ALP <1.5 × ULN	ALP ≥3 × ULN
TBL <1.5 × ULN	TBL ≥2 × ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5 × ULN	ALT or AST ≥2 × baseline with hepatic signs/symptoms*, or ALT or AST ≥3 × baseline
ALP ≥1.5 × ULN	ALP ≥2 × baseline
TBL ≥1.5 × ULN	TBL ≥1.5 × baseline (except for participants with Gilbert's syndrome)

* Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated CP, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection in study participants who have abnormal liver test results during the study

Additional safety data collection in hepatic safety eCRF should be performed in study participants who meet 1 or more of the following conditions:

- Elevation of serum ALT to ≥5 × ULN on 2 or more consecutive blood tests (if baseline ALT <1.5× ULN)
    - In participants with baseline ALT ≥1.5 × ULN, the threshold is ALT ≥3 × baseline on 2 or more consecutive tests
- Elevated serum TBL to ≥2 × ULN (if baseline TBL <1.5 × ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5 × ULN, the threshold should be TBL ≥2 × baseline
- Elevation of serum ALP to ≥2 × ULN on 2 or more consecutive blood tests (if baseline ALP <1.5 × ULN)
    - In participants with baseline ALP ≥1.5 × ULN, the threshold is ALP ≥2 × baseline on 2 or more consecutive blood tests
- Hepatic event considered to be an SAE
- Discontinuation of study drug due to a hepatic event.

Note: The interval between the 2 consecutive blood tests should be at least 2 days.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

Investigators are responsible for monitoring the safety of participants 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 participant.

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

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until participation in study has ended.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event eCRF.

Although all AEs after signing the ICF are recorded by the site in the eCRF, SAE reporting to sponsor begins after the participant has signed the ICF and has received study drug. However, if

an SAE occurs after signing the ICF, but prior to receiving lasmiditan, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until study end.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 3 (Section 10.3) to collect data on the outcome for both mother and fetus.

8.3.6. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a trial intervention.

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

Participants will 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.

Note: AEs/SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Appendix 3 (Section 10.3) of the protocol.

8.3.6.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug provided for the study, the investigator will promptly notify the sponsor.

8.3.6.2. Prompt Reporting of Product Complaints to Sponsor

Product complaints will be reported to the sponsor within 24 hours after the investigator becomes aware of the complaint.

The Product Complaint Form will be sent to the sponsor by email. If email is unavailable, then fax should be utilized.

8.3.6.3. Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

For this study, any dose of lasmiditan greater than 100 mg within a 24-hour time period will be considered an overdose.

There is no specific antidote for lasmiditan.

In the event of an overdose, the investigator/treating physician should:

1. Contact the Lilly CP immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 2 days).
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the investigator in consultation with the Lilly CP based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Venous blood samples of approximately 2 mL will be collected for measurement of plasma concentrations of lasmiditan and M8, as specified in the SoA (Section 1.3).

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor.

Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

8.5.1. 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 M8 will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

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

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

A blood sample for DNA isolation will be collected from participants.

See Appendix 5 (Section 10.5) for information regarding genetic research.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.10. Health Economics

This section is not applicable for this study.

8.11. Product Acceptability and Palatability Assessments

The participant will be asked to provide responses to questions designed to assess the acceptability and palatability of the OD tablet when administered with and without water. The questionnaire will assess the participant's experience relating to the taste, smell, mouthfeel, aftertaste, and the approximate disintegration time of the OD tablet in the oral cavity.

The questionnaire will be completed by the participant immediately after administration of the OD tablet both with and without water.

9. Statistical Considerations

9.1. Statistical Hypotheses

Bioequivalence of the OD tablet without water versus the current IR tablet will be established if the 90% confidence interval (CI) of the ratio of geometric least square means for area under the concentration versus time curve (AUC) from time zero to infinity (AUC[(0-∞]), AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), and maximum observed drug concentration (C_{max}) is within the testing boundaries of 0.8 and 1.25.

9.2. Sample Size Determination

A total of 36 participants are required complete the study to establish equivalence between the OD tablet formulation without water and the current IR tablet, based on the PK parameters measured.

Given the 6×3 design this would mean at least 6 participants would be randomly assigned to each of the 6 dosing sequences. The calculated total number of participants assumes 90% power for the two one-sided test (TOST) for equivalence with a significance level of 5%, analogous to a 90% CI. Further, this is based on:

- a nominally assigned true mean ratio of 1.05
- a coefficient of variation for C_{max} of 24.1%
- ratio testing boundaries of 0.8 and 1.25.

Assuming that 25% of participants will drop out or fail to provide full study data, approximately 48 participants should be enrolled to ensure that 36 participants, 6 per treatment sequence, will complete the study.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Enrolled	All participants randomly assigned to study intervention.
Safety	All enrolled participants who received at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic Analysis	All enrolled participants who received at least 1 dose of study intervention and have evaluable PK data.

9.3.1. Study Participant Disposition

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

9.3.2. Study Participant Characteristics

The participants' age, sex, weight, height, body mass index, race, and other demographic characteristics will be recorded and summarized using descriptive statistics.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of the sponsor or its designee.

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The SAP will be finalized prior to the first participant visit and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

Data listings will be provided for all data that are databased. Data listings will be provided for all participants up to the point of withdrawal, with any participants excluded from the relevant population highlighted.

Summary statistics and statistical analysis will only be presented for data where detailed in the SAP. Summary statistics and statistical analyses will generally only be performed for participants included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan and M8, based on plasma concentrations, will be calculated by standard noncompartmental methods of analysis and summarized using descriptive statistics.

The primary PK parameters for analysis will be C_{max}, AUC(0-∞), and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]) of lasmiditan.

Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

9.4.2.2. Pharmacokinetic Statistical Inference

Log-transformed AUC(0-∞), AUC(0-t_{last}), and C_{max} of lasmiditan will be evaluated in a linear mixed-effects model with fixed effects for period, sequence, and treatment and a random effect for participant within sequence.

All valid PK data will be included, whether or not the participants completed all 3 periods.

Estimates of geometric least square mean ratios together with the corresponding 90% CIs will be derived for the comparisons of AUC(0-∞), AUC(0-t_{last}), and C_{max} as follows:

- Primary endpoint: lasmiditan OD tablet without water (test) versus lasmiditan IR tablet

- Secondary endpoint: lasmiditan OD tablet with water (test) versus lasmiditan IR tablet.

The 2 lasmiditan formulations will be considered bioequivalent if the 90% CIs of the ratio of geometric least square means falls completely within 0.80 to 1.25.

Values of t_{max} will be analyzed non-parametrically using the Wilcoxon signed rank test. Estimates of the median difference between test and reference formulations based on the observed medians, 90% CIs, and the p-value from the Wilcoxon test will be calculated.

Additional PK analyses may be conducted if deemed appropriate.

9.4.3. Safety Analyses

9.4.3.1. Clinical Evaluation of Safety

All study intervention 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 study intervention 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 study intervention-related SAEs will be reported.

9.4.3.2. Statistical Evaluation of Safety

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

9.4.4. Product Acceptability and Palatability Analyses

Responses from the product acceptability and palatability questionnaire will be summarized categorically (frequency and percentage).

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

9.6. Data Monitoring Committee (DMC)

Not applicable to this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.3. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of Suspended or Terminated Dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (for example, by phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly personnel prior to any further planned dosing. If a dose is planned imminently, Lilly personnel will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture system will be stored at a third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

Data from complaint forms submitted to sponsor will be encoded and stored in the global product complaint management system.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.5.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and assures appropriate participant therapy and/or follow-up.

10.1.8. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Pregnancy testing will be conducted as detailed in the SoA (Section 1.3).

Investigators must document their review of each laboratory safety report.

Clinical Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus/Phosphate
Leukocytes (WBC)	Glucose (fasting)
Platelets	Blood urea nitrogen
Differential WBC (absolute counts and %) of:	Creatinine
Neutrophils	Uric acid
Lymphocytes	Total protein
Monocytes	Albumin
Eosinophils	Total bilirubin[a]
Basophils	Alkaline phosphatase
	Aspartate aminotransferase
Urinalysis	Alanine aminotransferase
Specific gravity	
pH	Ethanol testing[b]
Protein	Urine drug screen[b]
Glucose	Hepatitis B surface antigen[c]
Ketones	Hepatitis C antibody[c,d]
Bilirubin	HIV[c]
Urobilinogen	
Blood	Serum pregnancy test (all females)[c]
Nitrite	Urine pregnancy test (all females)[e]
Microscopic examination of sediment[f]	FSH (postmenopausal females only)[c]

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

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto-calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

[b] Performed at screening and admission to the clinical research unit (CRU; Day -1).

[c] Performed at screening only.

[d] Participants with a positive hepatitis C antibody test result can have a confirmatory hepatitis C RNA test.

[e] Performed for all females on admission to CRU (Day -1). A positive urine test will be confirmed with a serum pregnancy test.

[f] Test only if dipstick result is abnormal.

10.2.1. 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-LAIA 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	6	75
Pharmacokinetics	2	51[b]	102
Pharmacogenetics	10	1	10
Total			206.5
Total for clinical purposes			210

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

b Includes additional 3 samples, if required.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to the sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the sponsor or designee.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE report within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAE Report.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Females of Childbearing Potential
A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females NOT of Childbearing Potential

Females in the following categories are considered not of childbearing potential:

1. Infertile due to surgical sterilization
   - Documented hysterectomy
   - Documented bilateral oophorectomy
   - Document bilateral tubal ligation
2. Permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis.)

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female defined as either:
   - a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 12 months without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/L
   - a woman 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea
   - a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone-replacement therapy.

10.4.2. Contraception Guidance

10.4.2.1. Female Participants

All females must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure. A positive urine test will be confirmed with a serum pregnancy test.

Female participants not of childbearing potential are not required to adhere to contraceptive requirements.

Female participants of childbearing potential must agree to use either 1 highly effective method of contraception (<1% failure rate), or a combination of 2 effective methods of contraception, see Section 10.4.3, during the study and until 30 days after the last dose of study medication.

10.4.2.2. Male Participants

Male participants are not required to adhere to contraceptive requirements.

10.4.3. Contraception Methods

Abstinence

Participants who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) must agree to remain abstinent without sexual relationships with the opposite sex.

Same-sex relationships

Participants who are in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to stay in a same-sex relationship without sexual relationships with the opposite sex. Participants who are in exclusively same-sex relationships as their preferred and usual lifestyle are not required to use contraception.

Highly effective and effective contraception methods

Highly effective methods of contraception (less than 1% failure rate)	
Combined oral contraceptive pill and mini-pill	Intrauterine device (such as Mirena® and ParaGard®)
NuvaRing®	Contraceptive patch – ONLY women less than 198 pounds (90 kg)
Implantable contraceptives	Vasectomy – for partners of female participants
Injectable contraceptives (such as Depo-Provera®)	Fallopian tube implants (Essure®) if confirmed by hysterosalpingogram
Total abstinence	
Effective methods of contraception (use 2 forms combined except where noted)	
Male condom with spermicide[a]	Cervical sponge
Female condom with spermicide[a]	Cervical cap with spermicide
Diaphragm with spermicide	

[a] Male and female condoms should not be used in combination.

Unacceptable contraception methods

Unacceptable methods of contraception include

- periodic abstinence, such as
  - calendar
  - ovulation
  - symptothermal
  - post-ovulation methods
- declaration of abstinence just for the duration of the study
- withdrawal.

10.4.4. Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive lasmiditan.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported including fetal status (presence or absence of anomalies) and indication for the procedure.

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, including fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study intervention, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to lasmiditan or migraine and related diseases. They may also be used to develop tests/assays including diagnostic tests related to lasmiditan and/or interventions of this drug class and migraine. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to lasmiditan or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on lasmiditan continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

See Section 8.2.5.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, international normalized ratio (INR) (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]

HBV DNA [d]	Anti-actin antibody [b]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [d]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed ONLY by investigator-designated local laboratory; no central testing available.

[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

10.7. Appendix 7: Abbreviations

Term	Definition
5-HT	5-hydroxytryptamine
AE	adverse event
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 zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
CFR	Code of Federal Regulations
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 study-related, good clinical practice (GCP), and applicable regulatory requirements.
CP	clinical pharmacologist
CRF	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
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.

GCP	good clinical practice
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a participant 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, 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.
IR	immediate-release
IRB	Institutional Review Board
M8	metabolite 8
OD	oral-disintegrating
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.
PK	pharmacokinetic(s)
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
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.
SoA	Schedule of Activities
$t_{1/2}$	terminal half-life
TBL	total bilirubin
t_{max}	time of maximum observed drug concentration
ULN	upper limit of normal

11. References

None cited.

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