Protocol H8H-MC-LAIF(a) A Phase 1, Randomized, Subject- and Investigator-Blink,Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Stimulated Driving Performance in Healthy Volunteers

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A Phase I, Randomized, Subject- and Investigator-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Simulated Driving Performance in Healthy Volunteers

Lasmiditan (LY573144)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly:
15 February 2018
Amendment (a) Electronically Signed and Approved by Lilly on approval date provided below.

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1. Protocol Synopsis

Title of Study:

Protocol H8H-MC-LAIF: A Phase I, Randomized, Subject- and Investigator-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Simulated Driving Performance in Healthy Volunteers

Rationale:

Lasmiditan is a highly selective and potent agonist at the 5-hydroxytryptamine$_{1F}$ receptor and is under development as a neurally acting acute treatment for migraine. The most frequently reported adverse events (AEs) identified in the lasmiditan clinical development program are central nervous system in nature based on the mechanism of action of the drug. Due to treatment-related adverse effects of dizziness and fatigue observed in the Phase 2 clinical program, Study COL-MIG-106/H8H-MC-LAHG evaluated the impact of lasmiditan on driving performance at 90 minutes postdose. The results of this study showed impaired driving performance, but the duration of the impairment could not be estimated. The primary objective of the current study is to determine the duration of effect of lasmiditan compared to placebo on simulated driving performance in healthy subjects as measured by standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim) at 8, 12, and 24 hours after dosing.

Objectives	**Endpoints**
Primary To determine the duration of effect of acute doses of lasmiditan 100 mg and 200 mg compared to placebo on simulated driving performance in healthy subjects	Standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim) at 8, 12, and 24 hours postdose
Secondary To determine the effects of lasmiditan 100 mg, and 200 mg compared to placebo on	
• self-reported endpoints	• Sleepiness endpoint - KSS • Self-reported readiness to drive ("Right now do you feel safe to drive?) • VAS to assess subject's motivation and self-appraisal of their driving performance
• performance endpoints, and	CogScreen SDC test • Number of correct responses • Response accuracy • Standard deviation of reaction time
• driving performance endpoints.	• Lane exceedance; including number, maximum, duration, and area of exceedance • Average speed, speed deviation, speed count • Excessive Ay (cornering speed threshold exceeded) • Total collisions • Divided attention (DA): correct responses, omission errors, commission errors, reaction time, standard deviation of reaction times
To evaluate the PK of lasmiditan in healthy subjects	• PK parameters:

following a single 100- or 200-mg oral dose of lasmiditan	○ C_{max}, ○ t_{max}, and ○ AUC(0-∞)

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; DA = divided attention; KSS = Karolinska Sleepiness Scale; PK = pharmacokinetics; SDC = Symbol Digit Coding; t_{max} = time of maximum observed drug concentration; VAS = Visual Analog Scale.

Summary of Study Design:

Study H8H-MC-LAIF is a multicenter, randomized, subject- and investigator-blind, active- and placebo-controlled Williams square design with 4-period (full) crossover using lasmiditan 200 mg, lasmiditan 100 mg, and diphenhydramine 50 mg. Subjects will be randomized to treatment sequences and will complete all 4 periods within that treatment sequence.

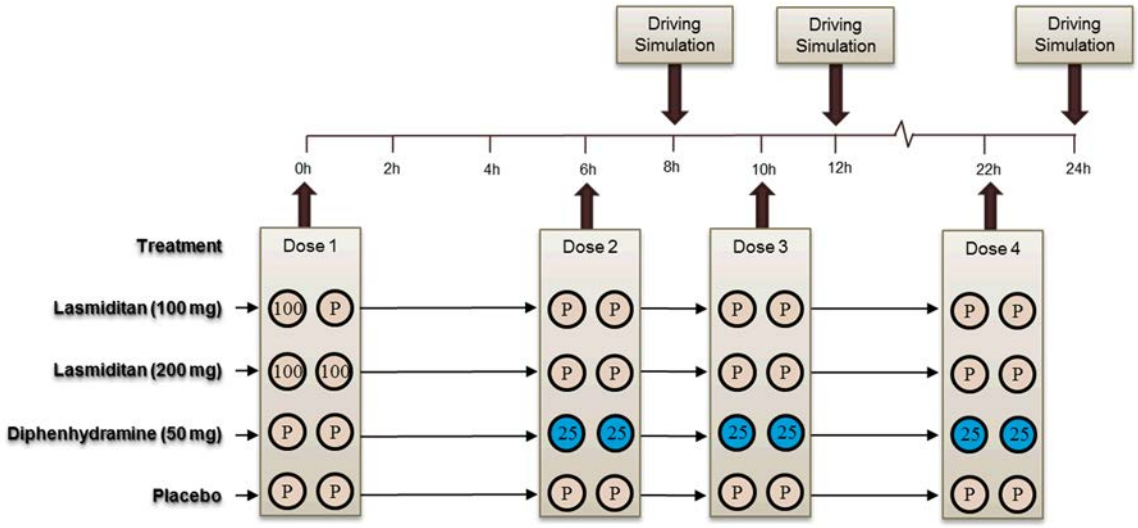
Each period will be of 3 days duration. It is anticipated that Study Periods 1, 2, 3, and 4 will commence on Study Days 1, 4, 7, and 10, respectively. For logistical reasons, the interval between periods may be extended by up to 2 days to accommodate site schedules. The minimum washout between periods is 3 days.

Screening (Visit 1) will include procedures to access subject eligibility including clinical laboratory tests, physical examination, and driving simulation training/screening. Prior to randomization, subjects will be screened for simulator sickness and will receive standardized training on the driving simulator and cognitive test battery. Screening procedures and screening assessments may be performed on different days but must be completed within 28 days before Period 1 (Visit 2). The training drives on the driving simulator must be completed no more than 21 days prior to the first dose of study drug.

Study drug or placebo will be administered by site staff during each period at 0 (Dose 1), 6 (Dose 2), and 10 (Dose 3) hours on Day 1 and at 22 hours (Dose 4) on Day 2 according to the treatment sequence assigned. Subjects will wear a blindfold when taking each dose to maintain the blind. The tablet size and shape are deemed similar enough to maintain the blind provided the subject is blindfolded. Driving assessments commence at 8, 12, and 24 hours after Dose 1.

The positive control (diphenhydramine 50 mg) is included to establish the sensitivity of the study endpoints.

Treatment Arms:



Treatment Sequences:

Subjects will be assigned and dosed with study medication (lasmiditan, diphenhydramine, or placebo) according to the treatment sequence they are randomized to. Subjects will be randomized equally into 1 of 4 treatment sequences:

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

Duration of Study:

On Day -1, prior to the first dose administration (the evening of clinical research unit [CRU] admission) subjects will complete a 20-minute practice drive on the CRCDS-MiniSim and a practice trial on the CogScreen SDC test.

Period 1, Day 1 subjects will be administered Dose 1 between approximately 0700 hours (7:00 AM) and 1000 hours (10:00 AM). On subsequent dosing days of Periods 2 to 4, doses will be administered at approximately the same time of day as doses in Period 1.

Approximately 8 hours following Dose 1, subjects will perform the CogScreen SDC test, KSS, and indicate their self-perceived safety to drive. Subjects will then perform the Country Vigilance-Divided Attention driving scenario on the CRCDS-MiniSim. Upon completion of the driving scenario, subjects will be administered a VAS to assess subjects' motivation and self-appraisal of their driving performance. Subjects repeat this testing procedure at approximately 12 hours and 24 hours after Dose 1 in all dosing periods.

While resident at the CRU, lights out will occur at approximately 2300 hours (11:00 PM) every night.

Subjects will remain a resident of the CRU from admission until discharge following the completion of study assessments. Blood draws for PK will be taken at pre- and post-dose according to the schedule of activities in all periods.

The total duration of subject participation will be approximately 5 weeks (range 3 to 7 weeks).

Number of Subjects:
Approximately 72 subjects will be enrolled so that 60 healthy volunteers complete the study. This will lead to 90% or more power for testing each of the hypotheses of primary interest regarding the driving assessment endpoints.

Statistical Analysis:

Safety:

Safety analysis will be based on all subjects enrolled who receive at least 1 dose of study medication. The safety analysis will evaluate AEs and additional safety parameters. The number and percentage of subjects experiencing at least 1 AE will be summarized by body system, preferred term, and treatment. If appropriate, AEs will also be summarized by intensity and relationship to study drug. Serious adverse events, if any, will be tabulated. Additional safety parameters will be assessed from summaries of physical examinations, 12-lead electrocardiograms and vital signs. Hematology, chemistry, and urinalysis laboratory test results will be categorized relative to the normal ranges. The changes from baseline for each of these parameters at postdose time points will be presented. Complete listings and summary tables for all safety information including AEs, laboratory safety data, vital signs, and physical examination will be included in the study report.

Pharmacokinetics:

Pharmacokinetic parameter estimates for lasmiditan and its metabolites will be calculated using standard noncompartmental methods of analysis and summarized using descriptive statistics. Plasma concentrations of diphenhydramine will be listed and summarized using descriptive statistics.

Pharmacodynamics:

The primary endpoint, SDLP, will be analyzed using a mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence for each of the driving time points. Secondary endpoints will be evaluated similarly; however, Lane Exceedance will be log transformed (more specifically ln[x+1]) prior to analyses. Pairwise comparisons for readiness to drive will be analyzed using McNemar test.

Graphical analyses will be performed to explore the relationship between PK concentrations with SDLP and/or other pharmacodynamic (PD) measures. Additional analyses may be performed to further characterize the PK/PD relationship(s), if warranted.

2. Schedule of Activities

Screening		Study Informed Consent
		Medical History
		Subject Eligibility
		Weight/Height (BMI)
		Drug and Alcohol Screen (repeat alcohol screen prior to Driving Sim Training/Practice if performed at a separate visit)
		Vital Signs
		Physical Examination (may be performed through Day -1)
		Epworth Sleepiness Scale
		Clinical Laboratory Tests
		Twelve-Lead ECG
		Temperature
		Serum Pregnancy Test (females only)
		CogScreen SDC Training/Screening
		Driving Sim Training/Screening
		Simulator Sickness Questionnaire
		Concomitant Medication assessment
Day -1 (Period 1)	Admission to Clinic	
		Confirm Subject Eligibility
		Drug and Alcohol Screen
		Serum Pregnancy Test (females only)
		Vital Signs
		Directed Physical Examination (symptom driven)
		CogScreen SDC Practice
		Driving Sim Practice
		Adverse Event Assessment
		Concomitant Medication Assessment (monitor throughout study)
Day 1 (Periods 1-4)	Predose	
		Vital Signs
		Directed Physical Examination (symptom driven)
		Lasmiditan and Metabolites PK Sampling (predose)
		Diphenhydramine PK Sampling (predose)
	+0.0 h	Study Drug Administration (Dose 1)
	+0.5 h	Lasmiditan and Metabolites PK Sample[a]
	+1.0 h	
		Lasmiditan and Metabolites PK Sample[a]
		Breakfast
	+1.5 h	Lasmiditan and Metabolites PK Sample[a]
	+2.0 h	Vital Signs/Lasmiditan and Metabolites PK Sample[a]
	+3.0 h	Lasmiditan and Metabolites PK Sample[a]
	+4.0 h	
		Vital Signs/Lasmiditan and Metabolites PK Sample[a]
		Lunch
	+6.0 h	

		Lasmiditan and Metabolites PK Sample[a]
		Study Drug Administration (Dose 2)
	+8.0 h	
		KSS[b]
		Adverse Event Assessment[b]
		CogScreen SDC Test[b]
		Self-Perceived Questionnaire (safe to drive)
		Lasmiditan and Metabolites PK Sample[a]
		Diphenhydramine PK Sample[a]
		CVDA Drive
		VAS (immediately after drive)
	+10.0 h	
		Lasmiditan and Metabolites PK Sample[a]
		Study Drug Administration (Dose 3)
	+11.0 h	Dinner
	+12.0 h	
		KSS[b]
		Adverse Event Assessment[b]
		CogScreen SDC Test[b]
		Self-Perceived Questionnaire (safe to drive)
		Lasmiditan and Metabolites PK Sample[a]
		Diphenhydramine PK Sample[a]
		CVDA Drive
		VAS (immediately after drive)
Day 2 (Periods 1-4)	+22 h	Study Drug Administration (Dose 4)
	+23 h	Breakfast
	+24 h	
		KSS[b]
		Adverse Event Assessment[b]
		CogScreen SDC Test[b]
		Self-Perceived Questionnaire (safe to drive)
		Lasmiditan and Metabolites PK Sample[a]
		Diphenhydramine PK Sample[a`]
		CVDA Drive
		VAS (immediately after drive)
	+36 h	Lasmiditan and Metabolites PK Sample[a]
Day 3 (Periods 1-4)	+48 h	Lasmiditan and Metabolites PK Sample[a]
Discharge (Day 3, Period 4)	Discharge from Clinical Unit	
		Vital Signs
		Physical Examination
		Clinical Laboratory Tests
		Adverse Event Assessment
		Concomitant Medication Assessment
Early Discontinuation		
		Vital Signs

		Physical Examination
		Clinical Laboratory Tests
		Twelve-Lead ECG
		Urinalysis Samples
		Serum Pregnancy Test (females only)
		Adverse Event Assessment
		Concomitant Medication assessment
Within 5 to 9 days after Discharge	Follow-up	
		Vital Signs
		Physical Examination
		Clinical Laboratory Tests
		Twelve-Lead ECG
		Urinalysis Samples
		Serum Pregnancy Test (females only)
		Adverse Event Assessment
		Concomitant Medication Assessment

Abbreviations: BMI = body mass index; CVDA = Country Vigilance-Divided Attention; ECG = electrocardiogram; h = hours, KSS = Karolinska Sleepiness Scale; PK = pharmacokinetic; SDC = Symbol Digit Coding; VAS = Visual Analog Scale.

a Pharmacokinetic and pharmacodynamic sampling times are given as targets to be achieved within reasonable limits. For PK sampling scheduled prior to driving assessments, the sampling window should be within -5 min to avoid conflict with driving assessment. Otherwise, the standard PK sampling windows: predose: -15 minutes; >0 to 2 hours postdose: ±5 minutes; 2.5 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes. The samples will be taken as per schedule to maintain the blind but samples will be analyzed according to the randomization table.

b This accompanying driving assessment procedure should occur within -30 minutes before the scheduled CVDA drive targeted for this sampling time

3. Introduction

Lasmiditan is being developed by Eli Lilly and Company (Lilly) for the acute treatment of migraine attacks with or without aura in adults. This molecule has been developed by Lilly as LY573144 and by CoLucid Pharmaceuticals, Inc. as COL-144 under the Investigational New Drug application 103420. Full details of lasmiditan's preclinical and clinical safety and tolerability information are contained in the Investigator's Brochure (IB).

3.1. Study Rationale

Lasmiditan is a highly selective and potent agonist at the 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor and is under development as a neurally acting treatment for migraine. The most frequently reported adverse events (AEs) identified in the lasmiditan clinical development program are central nervous system (CNS) in nature based on the mechanism of action of the drug. Due to treatment-related adverse effects of dizziness and fatigue observed in the Phase 2 clinical program, Study COL-MIG-106/H8H-MC-LAHG (106/LAHG) evaluating the impact of lasmiditan on driving performance was conducted in accordance with the United States Food and Drug Administration (FDA)'s Evaluating Drug Effects on the Ability to Operate a Motor Vehicle: Guidance for Industry (2017)

Study 106/LAHG was a randomized, subject-and investigator-blind, placebo-controlled, five-period, crossover study with the following treatments:

- Lasmiditan 50 mg
- Lasmiditan 100 mg
- Lasmiditan 200 mg
- Alprazolam 1 mg (positive control)
- Placebo

Subjects were randomized equally into 1 of 10 Latin square treatment sequences. The five periods were approximately 7 days in duration.

Period 1	→ Washout 1	→ Period 2	→ Washout 2	→ Period 3	→ Washout 3	→ Period 4	→ Washout 4	→ Period 5	→ EOS
Day 1	Days 2-6	Day 7	Days 8-13	Day 14	Days 15-20	Day 21	Days 22-27	Day 28	Day 35

The simulated driving test was commenced 90 minutes after dosing (on Days 1, 7, 14, 21, and 28).

The effect of lasmiditan on simulated driving performance was primarily measured by the standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator (CRCDS)-MiniSim. During testing, subjects were instructed to drive a 100-km highway segment with steady lane position and constant speed with a primary outcome measure of vehicle control, the SDLP (i.e. amount of "weaving" of the car in the lane).

Driving performance as assessed by SDLP was inferior for lasmiditan 50 mg, 100 mg, and 200 mg relative to placebo. This was further confirmed by symmetry analysis. A majority of

subjects exceeded the impairment threshold (4.4 cm, comparable to 0.05% blood alcohol count [BAC]) at even the lowest dose of lasmiditan. Sensitivity of the simulator and the model used in the research design were supported by significant findings on primary and secondary driving endpoints for alprazolam 1.0 mg.

Secondary driving endpoints provide further support to the conclusion that lasmiditan 50 mg, 100 mg, and 200 mg at 1.5 hours postdose had an adverse impact on simulated driving performance.

The time interval in 106/LAHG was chosen to capture the effect at the time of the peak concentration of lasmiditan and major metabolites M7 and M8, in accordance with the FDA guidance. However, the point at which patients should resume operation of a motor vehicle after taking lasmiditan is still unclear. The primary objective in the current study is to determine the duration of effect of lasmiditan compared to placebo on simulated driving performance in healthy subjects as measured by SDLP using the CRCDS-MiniSim at 8, 12, and 24 hours after dosing with lasmiditan. The 90-minute postdose simulated driving assessment used in 106/LAHG will not be repeated in the current study. For the positive control, diphenhydramine treatment doses will be administered 2 hours prior to driving assessments to ensure the maximum cognitive and sedative effect of the positive control (Ramaekers and O'Hanlon 1994).

3.2. Background

Lasmiditan is being investigated for the acute treatment of migraine in adults with and without aura. Lasmiditan is a high-affinity, highly selective 5-HT (serotonin)$_{1F}$ receptor agonist that is being developed as a novel therapy for the acute treatment of migraine. It has a chemical structure and pharmacologic profile that is distinct from the triptans, the current standard of care for the treatment of acute migraine. Lasmiditan does not contain the indole group observed in all triptans; instead it has a pyridinoyl-piperidine scaffold, which is unique to antimigraine medications. Lasmiditan is a low-molecular weight 5-HT$_{1F}$ receptor agonist with a nonvascular, primarily neural mechanism of action. It has high affinity for the human 5-HT$_{1F}$ receptor and >470-fold selectivity for the human 5-HT$_{1F}$ receptor relative to the 5-HT$_{1B}$ receptor. Across the completed Phase 1, 2, and 3 clinical studies, lasmiditan doses of 0.1 mg to 400 mg were evaluated in healthy subjects or patients with migraine. In two Phase 3, placebo-controlled studies in which patients treated 1 migraine attack with oral lasmiditan (50, 100, or 200 mg) or placebo, the most frequently reported lasmiditan treatment-emergent adverse events (TEAEs) were dizziness, paresthesia, somnolence, fatigue, lethargy, and nausea. A majority of these TEAEs were mild or moderate in severity. In healthy subjects, peak plasma concentrations of lasmiditan were observed approximately 1.5 hours to 2.5 hours after a single oral dose ranging from 25 mg to 400 mg, and the geometric mean terminal half-life was approximately 4 hours. Lasmiditan pharmacokinetics (PK) was approximately dose linear.

Following oral dosing with lasmiditan, up to 11 metabolites, including 3 major metabolites (M7, M8, and M18), were detected in human plasma and urine. These metabolites lacked significant pharmacological activity at the 5 HT$_{1F}$ receptor and were generally considered to be pharmacologically inactive. The relative proportions of metabolites to intact lasmiditan

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

3.3. Benefit/Risk Assessment

The primary objective of this study is to determine the duration of effect of lasmiditan on simulated driving performance in healthy subjects. There is no anticipated therapeutic benefit for the healthy subjects.

Lasmiditan has been generally well tolerated by healthy subjects as single oral doses up to 400 mg with no drug-related serious adverse events (SAEs) or withdrawals due to AEs in completed Phase 1 trials (as of 01 Nov 2017). Dosing of lasmiditan and diphenhydramine will be conducted in an inpatient setting, and subjects will be monitored in the clinical research unit (CRU) for the length of the study until discharge on Day 3, Period 4.

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

More detailed information about the known and expected benefits and risks of diphenhydramine may be found on the package information.

4. Objectives and Endpoints

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

Table LAIF.1. Objectives and Endpoints

Objectives	Endpoints
Primary To determine the duration of effect of acute doses of lasmiditan 100 mg and 200 mg compared to placebo on simulated driving performance in healthy subjects	Standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim) at 8, 12, and 24 hours postdose
Secondary To determine the effects of lasmiditan 100 mg and 200 mg compared to placebo on	
• self-reported endpoints	• Sleepiness endpoint - KSS • Self-reported readiness to drive ("Right now do you feel safe to drive?) • VAS to assess subject's motivation and self-appraisal of their driving performance
• performance endpoints, and	CogScreen SDC test • Number of correct responses • Response accuracy • Standard deviation of reaction time
• driving performance endpoints	• Lane exceedance, including number, maximum, duration, and area of exceedance • Average speed, speed deviation, speed count • Excessive Ay (cornering speed threshold exceeded) • Total collisions • DA: correct responses, omission errors, commission errors, reaction time, standard deviation of reaction times
To evaluate the PK of lasmiditan in healthy subjects following a single 100- or 200-mg oral dose of lasmiditan	• PK parameters: ○ C_{max}, ○ t_{max}, and ○ AUC(0-∞)
Exploratory To determine the effect of acute doses of lasmiditan 100 mg and 200 mg at 8, 12, and 24 hours compared with positive control (diphenhydramine 50 mg) at t_{max}	SDLP using the CRCDS-MiniSim at 8, 12, and 24 hours
To determine the effects of lasmiditan 100 mg and 200 mg compared with positive control (diphenhydramine 50 mg) on:	
• self-reported endpoints,	• Sleepiness endpoint - KSS • Self-reported readiness to drive ("Right now do you feel safe to drive?) • VAS to assess subject's motivation and self-appraisal of their driving performance

• performance endpoints, and	CogScreen SDC test • Number of correct responses • Response accuracy • Standard deviation of reaction time
• driving performance endpoints	• Lane exceedance, including number, maximum, duration, and area of exceedance • Average speed, speed deviation, speed count • Excessive Ay (cornering speed threshold exceeded) • Total collisions • Divided attention (DA): correct responses, omission errors, commission errors, reaction time, standard deviation of reaction times
To evaluate the PK of diphenhydramine	Diphenhydramine concentrations
To evaluate the PK of lasmiditan metabolites M8, M7, and M18	• PK parameters: ○ C_{max}, ○ t_{max}, and ○ AUC(0-∞)

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from zero to infinity; C_{max} = maximum observed drug concentration; CRCDS = Cognitive Research Corporation Driving Simulator; DA = divided attention; KSS = Karolinska Sleepiness Scale; PK = pharmacokinetics; SDC = Symbol Digit Coding; SDLP = standard deviation of lateral position; t_{max} = time of maximum observed drug concentration; VAS = Visual Analog Scale.

5. Study Design

5.1. Overall Design

This study is a multicenter, randomized, subject- and investigator-blind, active- and placebo-controlled Williams square design with 4-period (full) crossover using a single dose of lasmiditan (Figure LAIF.1). Subjects will be randomized to treatment sequences and should complete all 4 periods within that treatment sequence.

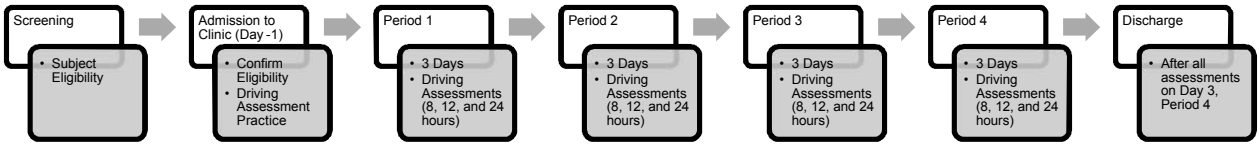


Figure LAIF.1. Study schematic.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Approximately 72 healthy subjects may be enrolled so that at least 60 healthy volunteers complete the study. For the purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been completed.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last subject.

5.4. Scientific Rationale for Study Design

Subjects will enter the CRU on Day -1. For the duration of the 4-period study, subjects will remain in the CRU. Each period will be of 3 days duration. It is anticipated that Study Periods 1, 2, 3, and 4 will commence on Study Days 1, 4, 7, and 10, respectively. For logistical reasons, the interval between periods may be extended by up to 2 days to accommodate site schedules. The minimum washout between periods is 3 days. Cognitive testing and driving simulation will be conducted approximately 8, 12, and 24 hours after Dose 1 on Day 1 of each study period. These driving assessment time points are expected to provide a wide range of responses including reversal of impairment.

The study design incorporates a positive control (diphenhydramine 50 mg) to confirm assay sensitivity. Per the FDA's Evaluating Drug Effects on the Ability to Operate a Motor Vehicle: Guidance for Industry (2017), sedating antihistamines are commonly used to understand the magnitude and duration of impairment. Diphenhydramine is a well-known sedating antihistamine available over the counter in the US and has been shown to have a significant

effect on driving performance (Kay et al. 1997, 2016). Diphenhydramine will be administered no more frequently than every 4 hours per package directions, coinciding with time points 2 hours prior to each driving assessment so that the maximum cognitive and sedative effect of the positive control coincide with the initiation of the driving simulation task.

5.5. Justification for Dose

The upper lasmiditan dose level of 200 mg has been generally well tolerated in previous studies on healthy subjects and patients enrolled in the completed Phase 3 program and is anticipated as the highest recommended dose for lasmiditan. The therapeutic dose range also includes 100 mg lasmiditan, which will be evaluated in the current study to explore any differences in the duration of driving impairment effect.

Diphenhydramine is an over-the-counter antihistamine medication for the treatment, as a temporary relief, of runny nose, itchy and watery eyes, sneezing and itching of the nose or throat due to hay fever or other upper respiratory allergies, or runny nose and/or sneezing due to common cold. The recommended dosage of diphenhydramine includes 50 mg taken every 4 to 6 hours. Urine drug screen and alcohol screen tests will be conducted on all potential subjects. Serum pregnancy tests will be conducted on all female subjects.

6. Study Population

Only medically healthy subjects with clinically acceptable laboratory profiles and electrocardiograms (ECGs) will be enrolled into the study. The informed consent documents will be discussed with each potential participant, and each individual will sign an informed consent document for the study prior to any study-specific procedures being performed.

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening procedures and screening assessments may be performed on different days but must be completed within 28 days prior to enrollment.

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

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening. Continued eligibility will be assessed through serum pregnancy (females only) and screening for alcohol and drugs of abuse on the day of admission.

[1] are overtly healthy males or females, as determined through medical history and physical examination.

[1a] male subjects:

are not required to adhere to contraceptive requirements.

[1b] female subjects:

of childbearing potential, must test negative for pregnancy at screening, and agree to use a reliable method of birth control during the study from admission and for 30 days following the last dose of study drug. Reliable methods of contraception for female subjects of childbearing potential include the use of stable hormonal contraception (including hormonal intrauterine devices) for at least 28 days prior to admission.

of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

of non-childbearing potential, i.e., postmenopausal or permanently sterile following hysterectomy, bilateral salpingectomy, or tubal ligation, as determined through medical history. Surgical tubal occlusion (i.e., Essure®) is also an acceptable form of surgical sterilization, provided the procedure was completed at least 3 months

prior to enrollment. Postmenopausal is defined as spontaneous amenorrhea for at least 12 months, and a follicle-stimulating hormone level greater than 40 mIU/mL, unless the subject is taking hormone replacement therapy (HRT).

[2] are between the ages of 21 and 50 years (inclusive). Attempts will be made to enroll no more than 60% of 1 gender in the study.

[3] are able to reliably perform study assessments (SDLP no higher than 1 standard deviation [SD] greater than the mean for normal healthy adults completing the practice scenario; Symbol Digit Coding [SDC] Correct no less than 1 SD below the mean for healthy adults in their age range); demonstrate the ability to understand task instructions; and are physically capable (e.g., adequate manual dexterity, vision, and hearing) and cognitively capable of performing study tasks.

[4] possess a valid driver's license and is an active drivers at screening. Driven a minimum of 8,000 miles (about 13,000 km) per year for the preceding 3 years.

[5] must also demonstrate sufficient simulator sickness questionnaire scores, which are not indicative of simulator sickness as defined in the driving simulation operations manual.

[6] have a regular sleep pattern, and in general, have at least 7 hours of sleep each night (bedtime occurs between 2100 hours and 2400 hours).

[7] have a score of <10 on the Epworth Sleepiness Scale.

[8] have a body mass index (BMI) of 18 kg/m^2 to 35 kg/m^2, inclusive

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

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

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

[12] are able and willing to give signed informed consent.

6.2. Exclusion Criteria

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

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

[14] are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.

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

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

[17] have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received the investigational product.

[18] have known allergies to lasmiditan, related compounds, or any components of the formulation, diphenhydramine, or a history of significant atopy.

[19] have an abnormal blood pressure (BP) and/or pulse rate as determined by the investigator.

[20] have a history or presence of or significant history of current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data. Appendectomy, splenectomy, and cholecystectomy are considered as acceptable.

[21] have a history within 3 months of admission, or current treatment for, a sleeping disorder (including excessive snoring, obstructive sleep apnea), or a chronic painful condition that interferes with the subject's sleep.

[22] have a history of difficulty either falling asleep or staying asleep in the previous 3 months of admission that is considered clinically significant by the investigator.

[23] have a history or diagnosis of any of the following conditions:

i. primary or secondary insomnia
ii. narcolepsy
iii. cataplexy (familial or idiopathic)
iv. circadian rhythm sleep disorder
v. parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and rapid eye movement behavior disorder
vi. sleep-related breathing disorder (obstructive or central sleep apnea syndrome, central alveolar hypoventilation syndrome)
vii. periodic limb movement disorder
viii. restless legs syndrome
ix. primary hypersomnia
x. excessive daytime sleepiness

xi. visual or auditory impairment which in the opinion of the investigator would interfere with study-related procedures or study conduct.

[24] are expected to use any other medication or dietary supplement to promote sleep including over the-counter sleep medications, during their participation in the study.

[25] consume excessive amounts of coffee, tea, cola, or other caffeinated beverages per day. Excessive amount is defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine).

[26] have traveled across 2 or more time zones (transmeridian travel) in the past 2 weeks prior to randomization.

[27] have worked in a night shift in the past 2 weeks prior to randomization.

[28] show a history of CNS conditions such as strokes, transient ischemic attacks, significant head trauma, seizures, CNS infections, migraine, brain surgery, or any other neurological conditions that, in the opinion of the investigator, increase the risk of participating in the study.

[29] have a known contraindication to diphenhydramine such as myasthenia gravis, epilepsy or seizure disorders, narrow-angle glaucoma, prostatic hypertrophy, urinary retention, asthma, bronchitis or chronic obstructive pulmonary disease.

[30] have a history of orthostatic hypotension, fainting spells, or blackouts that are considered clinically significant by the investigator.

[31] 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 HRT).

[32] show evidence of significant active neuropsychiatric disease (e.g., manic depressive illness, schizophrenia, depression) considered as clinically significant by the investigator.

[33] currently use or show evidence of substance abuse (including alcohol abuse) or dependence within the past 6 months based on history at screening visit.

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

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

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

[37] are women who are lactating.

[38] have donated blood of more than 500 mL within the previous 2 months of study screening.

[39] are smokers of more than 10 cigarettes or e-cigarettes, or 3 cigars or 3 pipes per day, and are unable to refrain from smoking while resident at the CRU.

[40] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females), or are unwilling to stop alcohol consumption 48 hours prior to admission in Period 1, and while resident at the CRU. At all other times, subjects must agree to consume no more than 2 units per day (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).

[41] consume alcohol on a regular basis (i.e., ≥5 times/week) within 2 hours of bedtime.

[42] inability to comply with the dietary regimen of the clinical research center.

[43] have a positive pregnancy test at screening or Day -1.

[44] are planning to become pregnant during the study or within 1 month of study completion.

[45] inability to use adequate contraception (as defined in [1] of the Inclusion Criteria) during the study. Female subjects must agree to use adequate contraception for 30 days following the last dose of study drug.

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [1] through [12] define a healthy population suitable for evaluation in this Phase 1 study. Criteria [13] and [14] prevent conflict of interest in study participants. Criteria [15] through [46] predominantly exclude medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

During each confinement period, subjects 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 subjects while resident at the CRU. Breakfast, lunch, and dinner will be provided according to the Schedule of Activities (Section 2).

6.3.2. Caffeine, Alcohol, and Tobacco

From 48 hours prior to admission in Period 1, and while resident at the CRU, subjects are not allowed to

- consume xanthine- or caffeine-containing food and drinks
- consume alcoholic beverages

  - At all other times, subjects must agree to consume no more than 2 units per day (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).

- use tobacco products

6.3.3. Activity

From 48 hours prior to admission in Period 1, and while resident at the CRU, subjects are not allowed to engage in strenuous activity.

While resident at the CRU, lights out will occur at approximately 2300 hours (11:00 PM) every night.

6.4. Screen Failures

Individuals who do not meet the driving simulation criteria (Inclusion Criteria [2] and [4] to [7]) for participation in this study (screen failure) may not be re-screened. Individuals who do not meet other criteria or driving simulation Inclusion Criterion [3] for participation in this study (screen failure) may be re-screened at the discretion of the investigator. Individuals may be re-screened 1 time. The interval between screenings should be at least 1 week. When the re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves orally administered lasmiditan with placebo. Diphenhydramine will be administered as a positive control. Table LAIF.2 shows the treatment regimens.

Lasmiditan, diphenhydramine, or placebo will be administered orally with approximately 240 mL of room temperature water according to the subject's assigned treatment sequence (Table LAIF.3) and at the time points specified in the Schedule of Activities (Section 2). Subjects will not be allowed to lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table LAIF.2. Treatments Administered

Treatment Name	Placebo	Lasmiditan (100 mg)	Lasmiditan (200 mg)	Diphenhydramine
Dosage Formulation	Tablet	Tablet	Tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s)	2 tablets	(1 × 100-mg) tablets/ 100 mg LY + 1 placebo tablet	(2 × 100-mg) tablets/ 200 mg LY	(2 × 25-mg) tablets/ 50 mg

Table LAIF.3. Treatment Schedule

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

The investigator or designee is responsible for

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

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

7.1.1. Packaging and Labeling

Each tablet of lasmiditan contains 100 mg of active ingredient and is provided as bulk supplies in bottles. Diphenhydramine will be sourced by the investigative site.

Both lasmiditan and diphenhydramine tablets are small and round. Placebo tablets are similar in size and shape to both lasmiditan and diphenhydramine tablets, but contain no active ingredient. Placebo tablets will be provided in similar bulk bottles as lasmiditan.

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

7.2. Method of Treatment Assignment

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

7.2.1. Selection and Timing of Doses

The doses will be administered at approximately the same time on each day (Figure LAIF.1). Period 1, Day 1 subjects will be administered Dose 1 between approximately 0700 hours (7:00 AM) and 1000 hours (10:00 AM). For each subject, the same time of Dose 1 in Period 1 should be targeted for Dose 1 in Periods 2 to 4 within reasonable limits. Subjects are permitted, and encouraged, to engage in their normal sleep pattern between Doses 3 and 4.

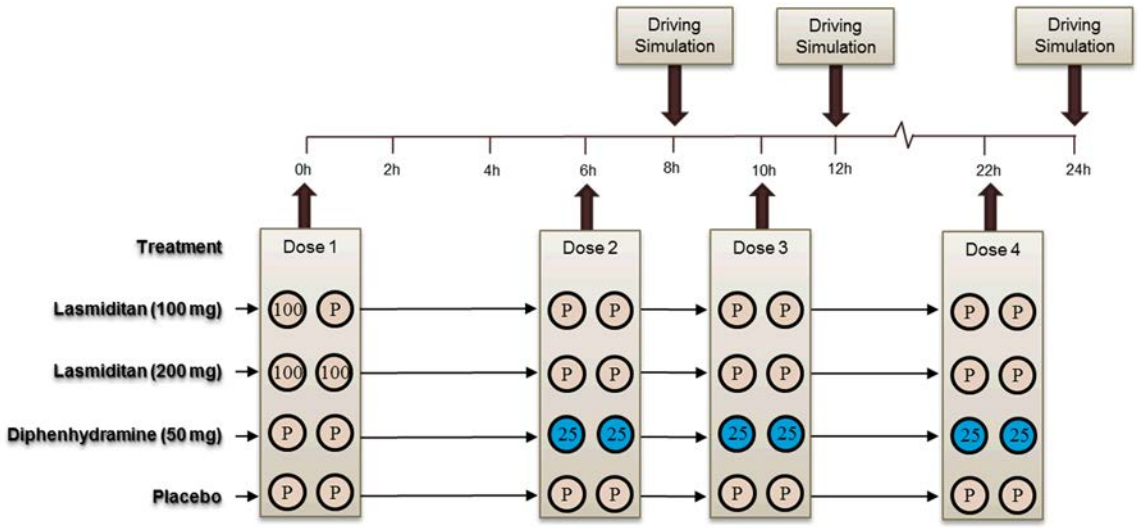


Figure LAIF.2 Timing of doses.

The actual time of all dose administrations will be recorded in the subject's case report form (CRF).

Treatment sequences will be determined using a repeated 4×4 Williams square design (Table LAIF.3). The randomization schedule will be securely maintained by the study center pharmacist who is responsible for dispensing the blinded study medication in accordance with the schedule. The sponsor (or designee) will be responsible for generating the randomization schedule and distributing them directly to the study center pharmacists.

7.3. Blinding

Study drugs (lasmiditan, diphenhydramine, and/or placebo) will be prepared into individual dispensing containers by an unblinded pharmacist or designee and administered by an unblinded staff member who will not be involved in any study assessment procedures. Each subject will be blindfolded prior to each dosing occasion to maintain the study blind. The unblinded staff member will hand the dispensing container to each subject, who will then self-administer all tablets in the dispensing container without touching any of the tablets by hand. Neither the investigator nor any study staff involved in the subject assessment will be allowed to witness the study drug administration. The blindfold will be removed before any assessments commence.

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

Emergency codes will be available to the investigator. A code, which reveals the treatment sequence for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study subject's emergency code.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted for medical management of the event. The subject's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Upon completion of the study, all codes must be returned to Lilly or its designee.

7.4. Dose Modification

Dose modification will not be allowed during the study

7.5. Preparation/Handling/Storage/Accountability

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

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

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

7.6. Treatment Compliance

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

7.7. Concomitant Therapy

In general, concomitant medications should be avoided; however, acetaminophen (maximum 3 g/24 hours) may be administered at the discretion of the investigator for the treatment of headache, etc. Contraceptive medication is permitted as per the inclusion criteria. Hormone replacement therapy is also allowed.

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

7.8. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

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

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

8.1. Discontinuation from Study Treatment

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

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

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

8.2. Discontinuation from the Study

Subjects will be discontinued under the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study

- Subject Decision
    - the subject requests to be withdrawn from the study.

8.3. Patients/Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing (including tolerance limits for timing).

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

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

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

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

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

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

9.2.1. Serious Adverse Events

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

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

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

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

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

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

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

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

9.3.1. Overdose of Lasmiditan

For the purposes of this study, an overdose of lasmiditan is considered any dose higher than the dose assigned through randomization. There is no specific antidote for lasmiditan.

In case of an overdose, it is recommended that the subject be monitored for signs and symptoms of adverse reactions. Subjects who develop adverse reactions should receive appropriate supportive therapy and AEs should be documented.

9.3.2. Overdose of Diphenhydramine

For the purposes of this study, an overdose of diphenhydramine is considered any dose higher than the dose assigned through randomization. Antihistamine overdosage reactions may vary from CNS depression to stimulation. Atropine-like signs and symptoms; dry mouth; fixed, dilated pupils; flushing; and gastrointestinal symptoms may also occur. In the event of a diphenhydramine overdose, the subject should receive appropriate medical care.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

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

Blood pressure and pulse rate should be measured singly after at least 5 minutes supine. For each individual subject, the same cuff size should be used throughout the study for the measurements of BP. The cuff should be attached to the subject'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, subjects should be supine for at least 5 minutes and then subjects will stand, and standing BP will be measured after

2 minutes; no longer than 3 minutes. If the subject feels unable to stand, supine vital signs only will be collected.

Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

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

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

For each subject, a single12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigative site.

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

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

9.4.4. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- adverse events

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

9.4.4.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly clinical pharmacologist or CRP. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests
- elevation of serum TBL to ≥2X ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests
- subject discontinued from the treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of lasmiditan and metabolites M7, M8, (S,R)-M18, and (S,S)-M18. Time of blood collection will be based on Dose 1. Similarly, at times specified in the Schedule of Activities (Section 2), 2 mL of venous blood samples will be collected to determine the plasma concentrations of diphenhydramine per Appendix 5 to confirm adequate washout and enable exploratory PK/pharmacodynamic (PD) analysis. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

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

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of lasmiditan and its metabolites M8, M7, and M18 will be assayed using a validated liquid chromatography tandem-mass spectrometry (LC-MS/MS) method. Analyses of lasmiditan samples collected from periods corresponding to placebo and positive control (diphenhydramine) are not planned with the exception of predose samples on Day 1 of each period.

Concentrations of diphenhydramine will be assayed using a validated LC-MS/MS method. Analyses of diphenhydramine samples collected from periods corresponding to placebo and lasmiditan are not planned with the exception of predose samples on Day 1 of each period.

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

9.6. Pharmacodynamics

9.6.1. Country Vigilance-Divided Attention Driving Scenario on the CRCDS-MiniSim

The present study employs the Country Vigilance-Divided Attention (CVDA) driving scenario, a 100-km two-lane highway driving task that includes a secondary visual vigilance task (DA). The monotonous Country Vigilance scenario has been demonstrated to be sensitive to detect the effects of fatigue or sleepiness on driving performance. This scenario has been useful in measuring the effects of sleep deprivation, obstructive sleep apnea, chronic primary insomnia, and is sensitive to CNS depressants (e.g., alcohol and sedating antihistamines). Results obtained using this methodology are comparable to those obtained using over-the-road driving tests (Siemen et al. 2015).

Subjects will perform the driving simulator test at the times specified in the Schedule of Activities (Section 2). Data will be captured in electronic format. Details are provided in the Cognitive Research Corporation CRCDS Testing Operations Manual.

9.6.2. Karolinska Sleepiness Scale

The Karolinska Sleepiness Scale (KSS) (Akerstedt and Gillberg 1990) will be used to assess subjective level of sleepiness. This is a subject self-reported measure of situational sleepiness and provides an assessment of alertness/sleepiness at a particular point in time. The KSS has been found to correlate with electroencephalogram and behavioral variables (Kaida et al. 2006).

Subjects will self-report their KSS assessments at the times specified in the Schedule of Activities (Section 2). The subject's self-reported scores will be recorded in the eCRF.

9.6.3. Self-Perceived Safety to Drive Question

Prior to driving, the subject will be asked a simple question as to whether they feel safe to drive ("Right now do you feel safe to drive?"). Subject will answer "yes" or "no". The answer will be recorded in the eCRF.

9.6.4. CogScreen Symbol Digit Coding

Symbol Digit Coding will be used in this study to measure attention, visual scanning, working memory, and speed of information processing. Symbol Digit Coding is a computer analog of the conventional symbol-substitution task found in the WAIS-R Digit Symbol subtest and the

Symbol Digit Modalities Test (Wechsler 1981). The SDC test will be administered by trained study site personnel. Subjects will perform the test prior to the driving simulation test at the times specified in Section 2. The subject will perform the test by interacting with an electronic monitor screen. Data will be captured in electronic format. Details are provided in the CogScreen® Examiner Manual, CogScreen LLC, 2016.

9.6.5. Visual Analog Scale to Assess Subject's Motivation and Self-Appraisal

After completing the driving simulation, subjects will assess their own performance and their level of motivation to perform at their best during the driving simulation.

Subjects will respond to 2 questions:

1. How well you think you drove for the last 60 minutes?
2. How motivated did you feel to drive at your best during the last 60 minutes of driving?

Subjects will record their response to each question by writing a vertical line on a 100-mm horizontal, linear visual analog scale, indicating their level of performance (Not Satisfactory to Satisfactory) and motivation (Not Motivated to Motivated). Scores on the 100-mm linear scale will be measured to the nearest millimeter from the left. The subject's scores will be recorded in the eCRF.

9.7. Genetics

This section is not applicable for this study.

9.8. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Approximately 72 subjects will be enrolled so that approximately 60 healthy volunteers complete this study. This study is designed to test noninferiority (NI) of lasmiditan relative to placebo, with a diphenhydramine test versus placebo to confirm the sensitivity of the simulator to detect treatment effects. The following assumptions were made in the sample size computation: (a) SD of differences between lasmiditan and placebo within subject for SDLP is approximately 9.5 cm; (b) the true difference between lasmiditan doses and placebo is 0; and (c) the NI margin is proposed to be 4.4 cm, which is the effect seen with 0.05% of BAC. Under these assumptions, a sample of 60 subjects would provide >90% power to establish NI of either dose of lasmiditan compared to placebo in terms of the primary end point, SDLP. This sample size is more than adequate to detect diphenhydramine differences, which are anticipated to exceed the NI margin, from placebo.

Subjects who are randomized but who do not complete all 4 periods during the Treatment Phase may be replaced. Replacement subjects will enter the same treatment sequence as the original subjects to complete all 4 periods.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

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

10.2.2. Study Participant Characteristics

The subjects' year of birth, sex, weight, height, race, and other demographic characteristics will be recorded. Age and BMI will be calculated. Demographic and baseline characteristics will be summarized.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee. Complete details of the planned analyses will be contained in the statistical analysis plan.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational products and have evaluable PK.

Pharmacodynamic analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational products and have evaluable PD.

Pharmacokinetic/pharmacodynamic analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational products and have evaluable PK.

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

Additional exploratory analyses of the data will be conducted as deemed appropriate. In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, SD, median, minimum, and maximum values.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

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

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

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include 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.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Plasma concentrations of lasmiditan, its metabolites, and diphenhydramine will be listed and summarized using descriptive statistics.

Pharmacokinetic parameter estimates for lasmiditan and its metabolites will be calculated using standard noncompartmental methods of analysis and summarized using descriptive statistics by dose level.

The primary parameters for analysis will be maximum observed drug concentration (C_{max}) and area under the concentration versus time curve (AUC). Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

10.3.3. Pharmacodynamic Analyses

The primary endpoint, SDLP, will be analyzed using a mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence for each of the driving time points. Separate models will be used for each of the driving time points.

Secondary endpoints will be evaluated similarly; however, Lane Exceedance will be log transformed (more specifically, ln[x+1]) prior to analyses. Pairwise comparisons for readiness to drive will be analyzed using McNemar test.

For the primary and secondary endpoints, pairwise comparisons (hypothesis tests) of differences in means, and 95% confidence intervals on differences will be provided at each time point for

1. Lasmiditan 100 mg versus placebo
2. Lasmiditan 200 mg versus placebo
3. Diphenhydramine 50 mg versus placebo

In addition, pairwise within-subject differences in SDLP greater than 4.4 cm in absolute value (equal to the previously found difference between placebo and 0.05% BAC for the CRCDS) will be compared using McNemar test. Furthermore, these pairwise, within-subject differences in SDLP will be tested for symmetry about zero using the maximally selected McNemar test.

10.3.3.1. Pharmacodynamic Statistical Inference

To address multiplicity of testing, 2 doses of lasmiditan versus placebo at 3 time points for the primary endpoint of SDLP, ascending doses of lasmiditan at descending time points will be interpreted in a sequential manner, starting with the 100-mg dose at 24 hours and proceeding to the 200-mg dose and earlier time points via a graphical multiple comparisons procedure (Figure LAIF.3). The value of w, the split of alpha after testing 100 mg at 24 hours, will be specified in the statistical analysis plan.

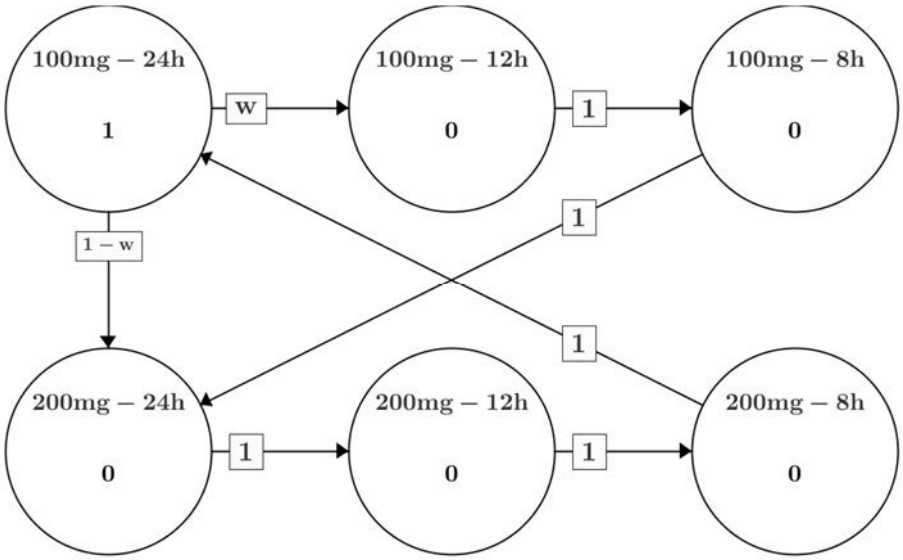


Figure LAIF.3. Pharmacodynamic statistical inference – graphical multiple comparisons procedure.

Doses of lasmiditan will be considered noninferior to placebo at a time point if the upper 95% confidence limit on the difference in SDLP between that dose and placebo is less than 4.4 cm. No adjustment to alpha levels will be made for the comparison of diphenhydramine either to placebo or to lasmiditan, or for secondary endpoints or analyses. Formal statistical tests (where performed) will be 2-sided with testing at the alpha=0.05 level of significance.

10.3.4. Pharmacokinetic/Pharmacodynamic Analyses

Graphical analyses may be performed to explore the relationship between PK concentrations with driving performance (i.e., SDLP) and/or other PD measures. Additional analyses may be performed to further characterize the PK/PD relationship(s), if warranted.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
BAC	blood alcohol count
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CNS	central nervous system
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.
CRCDS-MiniSim	Cognitive Research Corporation Driving Simulator-MiniSim
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
CVDA	Country Vigilance-Divided Attention
DA	Divided attention
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
GCP	good clinical practice
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
Investigational New Drug	An application to the FDA to allow testing of a new drug in humans.
informed consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
KSS	Karolinska Sleepiness Scale
LC-MS/MS	liquid chromatography tandem-mass spectrometry
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.
NI	noninferiority
PK/PD	pharmacokinetic/pharmacodynamic
randomize	The process of assigning subjects to an experimental group on a random basis.
SAE	serious adverse event
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SDC	Symbol Digit Coding
SDLP	standard deviation of lateral position
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
ULN	upper limit of normal
VAS	Visual Analog Scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate (total CO_2)
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Glucose (random)
Platelets	
Differential WBC (absolute counts) of	Blood urea nitrogen (BUN)
Neutrophils	Uric acid
Lymphocytes	
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
	Alkaline phosphatase (ALP)
Urinalysis[a]	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Creatinine
Protein	
Glucose	
Ketones	Ethanol testing[b]
Bilirubin	Urine drug screen[b]
Urobilinogen	Hepatitis B surface antigen [c]
Blood	Hepatitis C antibody [c]
Nitrite	HIV [c]
	Pregnancy test (females only)
	FSH (if applicable) [c]

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

[a] Performed at follow-up and early discontinuation only.

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

[c] Performed at screening only.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

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

Recruitment

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

Ethical Review

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

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

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

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

Regulatory Considerations

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

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

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

Protocol Signatures

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

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

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

If the coordinating investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

Data Quality Assurance

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

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

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

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; WBC = white blood cell.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol H8H-MC-LAIF 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	2	25
Lasmiditan and metabolite pharmacokinetics	2	52	104
Diphenhydramine pharmacokinetics	2	16	32
Total			180.5
Total for clinical purposes (rounded up to the nearest 10 mL)			190

Appendix 6. Protocol Amendment H8H-MC-LAIF(a) Summary: A Phase I, Randomized, Subject- and Investigator-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Simulated Driving Performance in Healthy Volunteers

Overview

Protocol H8H-MC-LAIF A Phase I, Randomized, Subject- and Investigator-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Simulated Driving Performance in Healthy Volunteers has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Pharmacogenetic blood sampling was removed from study in agreement with the Sponsor's Tailored Therapeutics group. The number of healthy volunteers is relatively small (<100) and a pharmacogenetic sample collection is unlikely to enable investigation of pharmacogenetic characteristics in migraine response to lasmiditan.

Revised Protocol Sections

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

2. Schedule of Activities

Screening		Study Informed Consent
		Medical History
		Subject Eligibility
		Weight/Height (BMI)
		Drug and Alcohol Screen (repeat alcohol screen prior to Driving Sim Training/Practice if performed at a separate visit)
		Vital Signs
		Physical Examination (may be performed through Day -1)
		Epworth Sleepiness Scale
		Clinical Laboratory Tests
		Twelve-Lead ECG
		Temperature
		Serum Pregnancy Test (females only)
		CogScreen SDC Training/Screening
		Driving Sim Training/Screening
		Simulator Sickness Questionnaire
		Concomitant Medication assessment
Day -1 (Period 1)	Admission to Clinic	
		~~Sample for Pharmacogenetic Analysis (prior to or on Day 1, Period 1)~~
		Confirm Subject Eligibility
		Drug and Alcohol Screen
		Serum Pregnancy Test (females only)
		Vital Signs
		Directed Physical Examination (symptom driven)
		CogScreen SDC Practice
		Driving Sim Practice
		Adverse Event Assessment
		Concomitant Medication Assessment (monitor throughout study)
Day 1 (Periods 1-4)	Predose	
		Vital Signs
		Directed Physical Examination (symptom driven)
		Lasmiditan and Metabolites PK Sampling (predose)
		Diphenhydramine PK Sampling (predose)
	+0.0 h	Study Drug Administration (Dose 1)
	+0.5 h	Lasmiditan and Metabolites PK Sample[a]
	+1.0 h	
		Lasmiditan and Metabolites PK Sample[a]
		Breakfast
	+1.5 h	Lasmiditan and Metabolites PK Sample[a]
	+2.0 h	Vital Signs/Lasmiditan and Metabolites PK Sample[a]
	+3.0 h	Lasmiditan and Metabolites PK Sample[a]
	+4.0 h	
		Vital Signs/Lasmiditan and Metabolites PK Sample[a]
		Lunch

	+6.0 h	
		Lasmiditan and Metabolites PK Sample[a]
		Study Drug Administration (Dose 2)
	+8.0 h	
		KSS[b]
		Adverse Event Assessment[b]
		CogScreen SDC Test[b]
		Self-Perceived Questionnaire (safe to drive)
		Lasmiditan and Metabolites PK Sample[a]
		Diphenhydramine PK Sample[a]
		CVDA Drive
		VAS (immediately after drive)
	+10.0 h	
		Lasmiditan and Metabolites PK Sample[a]
		Study Drug Administration (Dose 3)
	+11.0 h	Dinner
	+12.0 h	
		KSS[b]
		Adverse Event Assessment[b]
		CogScreen SDC Test[b]
		Self-Perceived Questionnaire (safe to drive)
		Lasmiditan and Metabolites PK Sample[a]
		Diphenhydramine PK Sample[a]
		CVDA Drive
		VAS (immediately after drive)
Day 2 (Periods 1-4)	+22 h	Study Drug Administration (Dose 4)
	+23 h	Breakfast
	+24 h	
		KSS[b]
		Adverse Event Assessment[b]
		CogScreen SDC Test[b]
		Self-Perceived Questionnaire (safe to drive)
		Lasmiditan and Metabolites PK Sample[a]
		Diphenhydramine PK Sample[a]`
		CVDA Drive
		VAS (immediately after drive)
	+36 h	Lasmiditan and Metabolites PK Sample[a]
Day 3 (Periods 1-4)	+48 h	Lasmiditan and Metabolites PK Sample[a]
Discharge (Day 3, Period 4)	Discharge from Clinical Unit	
		Vital Signs
		Physical Examination
		Clinical Laboratory Tests
		Adverse Event Assessment
		Concomitant Medication Assessment
Early Discontinuation		

		Vital Signs
		Physical Examination
		Clinical Laboratory Tests
		Twelve-Lead ECG
		Urinalysis Samples
		Serum Pregnancy Test (females only)
		Adverse Event Assessment
		Concomitant Medication assessment
Within 5 to 9 days after Discharge	Follow-up	
		Vital Signs
		Physical Examination
		Clinical Laboratory Tests
		Twelve-Lead ECG
		Urinalysis Samples
		Serum Pregnancy Test (females only)
		Adverse Event Assessment
		Concomitant Medication Assessment

Abbreviations: BMI = body mass index; CVDA = Country Vigilance-Divided Attention; ECG = electrocardiogram; h = hours, KSS = Karolinska Sleepiness Scale; PK = pharmacokinetic; SDC = Symbol Digit Coding; VAS = Visual Analog Scale.

a Pharmacokinetic and pharmacodynamic sampling times are given as targets to be achieved within reasonable limits. For PK sampling scheduled prior to driving assessments, the sampling window should be within -5 min to avoid conflict with driving assessment. Otherwise, the standard PK sampling windows: predose: -15 minutes; >0 to 2 hours postdose: ±5 minutes; 2.5 to 6 hours postdose: ±10 minutes; 7 to 12 hours postdose: ±20 minutes; >12 hours postdose: ±30 minutes. The samples will be taken as per schedule to maintain the blind but samples will be analyzed according to the randomization table.

b This accompanying driving assessment procedure should occur within -30 minutes before the scheduled CVDA drive targeted for this sampling time

9.7. Genetics

~~A blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2), where local regulations allow.~~

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

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

~~Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and/or IRBs impose shorter time limits, for the study at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response~~

~~to regulatory questions, and investigation of variable response that may not be observed until later in the development of lasmiditan or after lasmiditan is commercially available.~~

~~Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome-wide association studies, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.~~

This section is not applicable for this study.

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol H8H-MC-LAIF 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	2	25
Lasmiditan and metabolite pharmacokinetics	2	52	104
Diphenhydramine pharmacokinetics	2	16	32
~~Pharmacogenetics~~	~~10~~	~~1~~	~~10~~
Total			~~190.5~~180.5
Total for clinical purposes (rounded up to the nearest 10 mL)			~~200~~190