H8H-MC-LAIJ Protocol (b)

Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks

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Protocol H8H-MC-LAIJ(b)
Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks (CENTURION)

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Confidential Information

Lasmiditan (LY573144)

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1. Synopsis

Title of Study:

Protocol H8H-MC-LAIJ Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks (CENTURION)

Rationale:

In 2 Phase 3 single migraine attack studies, lasmiditan demonstrated statistically significant superiority versus placebo in the proportion of patients who were headache pain-free as well as the proportion of patients who were free of their migraine-associated most bothersome symptom (MBS) at 2 hours postdose. This global, multicenter, placebo-controlled, double-blind study will assess the efficacy, consistency of response, and safety of lasmiditan in acute treatment of 4 migraine attacks with or without aura.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on migraine headache pain freedom compared to placebo	• The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack
• To evaluate the consistency of response to lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 2 out of 3 attacks
Secondary	
Efficacy	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on freedom from MBS compared to placebo	• The proportion of patients in each group that are free of MBS associated with migraine at 2 hours postdose during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on pain relief compared to placebo	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours post dose during the first attack.
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on sustained freedom from pain compared to placebo	• The proportion of patients in each group with 24-hour and with 48-hour sustained pain freedom during the first attack defined as pain-free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication
• To evaluate the need for rescue medication in patients treated with lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group requiring rescue medication for migraine within 24 hours of treatment during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg at 2 hours on freedom from symptoms associated with migraine compared to placebo	• The proportion of patients in each group that are free of symptoms associated with migraine at 2 hours postdose during the first attack, including each of the following: phonophobia, photophobia, nausea, and vomiting

Objectives	Endpoints
Secondary, *Efficacy*, continued	
• To assess the probability of migraine relapse in patients treated with lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group with migraine recurrence at 24 and 48 hours during the first attack defined as return of any headache in patients who were pain-free at 2 hours.
• To explore the time course of lasmiditan 200 mg and 100 mg efficacy compared to placebo	• The proportion of patients in each group at each time point with pain freedom, pain relief, freedom from MBS, and no disability postdose during first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on migraine-related disability compared to placebo	• Mean change from baseline in total score and individual items as measured by the MIDAS scale, in each group at end of study
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on disability during migraine attacks compared to placebo	• The proportion of patients in each group with no disability as measured by the disability item, at 2 hours postdose during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on PGIC compared to placebo	• The proportion of patients in each group very much or much better as measured by PGIC, at 2 hours postdose during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on HRQoL during an acute migraine attack compared to placebo	• Mean HRQoL score for domains of social functioning, migraine symptoms, and feelings/concerns, as measured by the 24-hour MQoLQ, in each group at 24 hours postdose during first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on treatment satisfaction compared to control	• The proportion of patients in each group who are satisfied with their treatment at EoS as measured by a 4-item questionnaire
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on health utility compared to placebo	• Mean change from baseline in utility in each group as measured by the EQ-5D-5L, at 24 hours postdose during first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg in triptan nonresponders	• The proportions of patients in the subpopulation of triptan nonresponders that achieve primary and secondary objectives in each group during the first attack • The proportions of patients in the subpopulation of triptan nonresponders versus other patients that achieve primary and secondary objectives in each group during the first attack
Consistency	
• To evaluate the consistency of lasmiditan 200 mg and 100 mg on migraine headache pain relief in 2 out of 3 attacks compared to placebo	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose in at least 2 out of 3 attacks
• To evaluate the consistency of response to lasmiditan 200 mg and 100 mg in 3 out of 4 attacks compared to control	• The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 3 out of 4 attacks
• To evaluate the consistency of lasmiditan 200 mg and 100 mg on migraine headache pain relief in 3 out of 4 attacks compared to control	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose in at least 3 out of 4 attacks

Objectives	Endpoints
Secondary, *Consistency,* continued	
• To evaluate the consistency of lasmiditan 200 mg and 100 mg in triptan nonresponders.	• The proportions of patients in the subpopulation of triptan nonresponders versus other patients that achieve consistency in each group defined as pain freedom during 2 out of 3 attacks

Abbreviations: 24-hour MQoLQ = 24-Hour Migraine Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-dimension 5-level scale; HRQoL = Health-Related Quality of Life; MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment Test; PGIC = Patient Global Impression of Change.

Summary of Study Design:

Study H8H-MC-LAIJ is a prospective, multicenter, randomized, double-blind, modified-parallel, placebo-controlled Phase 3 study of adult patients suffering from migraine with or without aura.

Treatment Arms and Duration:

One treatment group will receive lasmiditan 200 mg for 4 attacks, 1 treatment group will receive lasmiditan 100 mg for 4 attacks, and a control group will receive placebo for 3 attacks and lasmiditan 50 mg for 1 attack. The control group will consist of 2 treatment sequence groups (1:1) where 1 group will receive lasmiditan for attack 3 and the other group will receive lasmiditan for attack 4.

For rescue (pain freedom not achieved) or recurrence (pain freedom achieved but then pain recurs), patients may take their own unexcluded medications beginning at least 2 hours postdose; patients MUST NOT take triptan, ergot, opioid, or barbiturate medications within 24 hours of taking study drug (that is, 24 hours before or after).

To avoid differential drop out which could compromise the validity of the study, patients should not be informed about the treatment groups; instead, patients should be informed that no patient will receive placebo for all attacks.

Number of Patients:

Approximately 2100 patients will be screened to achieve approximately 1600 patients randomized, approximately 1150 patients with data for first attack, and approximately 800 patients with data for consistency assessment. An additional 200 patients may be randomized if there is an insufficient number of patients with complete data for consistency assessment.

Statistical Analysis:

Efficacy analyses will be conducted on the intent-to-treat (ITT) population. This set includes all randomized patients who use at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity assessments at or before 2 hours postdose. The primary efficacy analysis will compare the proportion of patients with 2-hour pain freedom during the first attack in the lasmiditan 200-mg group with placebo and compare the proportions of patients with 2-hour pain freedom during the first attack in the lasmiditan 100-mg group with placebo.

The consistency analyses will be conducted on the ITT consistency population, a subset of the ITT population with sufficient evaluable attacks. To evaluate the primary consistency endpoint, the proportions of patients with 2-hour pain freedom during 2 out of the first 3 evaluable attacks in the lasmiditan 200-mg and 100-mg groups will be compared to the results of the evaluable attacks treated with placebo in the control group.

Primary and gated secondary endpoints will be analyzed in a multiple comparisons procedure that preserves overall type I error at the 1-sided significance level of 0.025. Tests of all other endpoints will be conducted at a 2-sided significance level of 0.05.

Safety analyses will be conducted on the safety population. This set includes all randomized patients who take at least 1 dose of study drug, regardless of whether or not they undergo any study assessments. Patients will be evaluated by the drug they used, not by the drug to which they were randomized.

2. Schedule of Activities

Table LAIJ.2.1. Schedule of Activities

	Visit 1[a] Screening	Visit 2 Baseline (at site)	Treatment Attack 1-4[b] All attacks: Mod/sev within 4 hrs of onset Attack 2: ≥48 hrs after dosing Attack 1 Attack 3: ≥48 hrs after dosing Attack 2 Attack 4: ≥48 hrs after dosing Attack 3			Visit 6 EoS (at site) or EDC[c]	Notes
		V1+3-30 days (pending lab results)	Visit 3 Phone Call 1 after Attack 1 or at 1 mo[d]±1 wk after V2	Visit 4 Site Visit at +2 mos±1 wk after V2	Visit 5 Phone Call 2 at 3 mos±1 wk after V2	≥7 days after last treated attack (=last dose) OR at 4 mos±2 wks after V2	
Obtain informed consent	X						
Inclusion and exclusion	X						
Introduce eDiary (V1) including assess patient capability to use eDiary	X						
Demographics	X						
Vital signs	X			X		X	Temperature, BP, pulse. BP/pulse measured sitting before blood draws, dosing. Use local BP equipment.
Weight	X					X	
Height	X						
Menstrual cycle status		X	X	X	X	X	Females asked to provide dates and durations of menstrual period; table included in paper journal to record between visits.
Review migraine history including prior treatment	X						
Review medical history and concomitant medication	X						
Physical examination	X					X	
Neurological exam	X					X	

Document migraine characteristics per IHS criteria	X						
Complete MIDAS	X					X	
C-SSRS - BL/screening version [e]	X						
C-SSRS - since last visit version [e]		X		X		X	
Self-Harm Supplement Form	X	X		X		X	
Self-Harm Follow-up Form [f]	X	X		X		X	
12-lead ECG	X						Patients must be supine for 5 to 10 min before ECG collection and remain supine but awake during collection.
Clinical laboratory (hematology, serum chemistry, urinalysis)	X			X		X	Hepatic algorithm triggered in cases of hepatic abnormalities identified by laboratory testing.
Serum pregnancy test or FSH	X			X		X	Pregnancy tests assessed in WOCBP (serum as indicated; urine more frequently if mandated by local regulations); FSH assessed as appropriate (details in Inclusion Criterion #7)
Urine drug screen	X						Can be repeated once if result is positive.
Pharmacogenetic sample (genetic sample/DNA)	X						
Confirm eligibility		X					
Patient training video		X					
Randomization		X					
Dispense study drug		X					
Provide study eDiary and provide detailed instructions and complete EQ-5D-5L		X					

Migraine attack (eDiary) documentation by patient		X	X				Patients enter data in eDiary during attacks (Appendix 7) and from V2 to EoS, will be reminded daily to record AEs and new conmeds in paper journal.
mTOQ-6		X					
HCRU		X				X	
Employment status		X				X	
Assessment of driving accidents/violations		X		X		X	
Treatment Satisfaction						X	
Verify any eDiary or study drug issues, assess compliance all procedures, provide instructions if needed			X	X	X		
Determine compliance study drug				X		X	
Documentation of rescue/recurrence medication			X	X	X	X	
Documentation of AEs and concomitant medication	X	X	X	X	X	X	
Collect unused/empty study drug pack and eDiary						X	

Abbreviations: 24-hour MQoLQ = 24-Hour Migraine Quality of Life Questionnaire; AE = adverse event; BP = blood pressure; conmed = concomitant medication; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EDC = early discontinuation; eDiary = electronic diary; EoS = end of study; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FSH = follicle-stimulating hormone; HCRU = Health Care Resource Utilization; hrs = hours; IHS = International Headache Society; MIDAS = Migraine Disability Assessment Test; min = minutes; mo/mos = month/months; mod = moderate; mTOQ-6 = Migraine Treatment Optimization Questionnaire; PGIC = Patient Global Impression of Change; QoL = quality of life; sev = severe; V = visit; WOCBP = women of child-bearing potential (see Inclusion Criterion #7 for details); wks = weeks.

[a] V1 activities to be collected outside migraine attack.

[b] Attacks treated do not need to be consecutive. Minimum amount of time between attacks is 48 hours (determined by timing of dosing, i.e., the next attack may not be treated with study drug within 48 hours of taking study drug). During the treatment period, unscheduled visits may be completed at the discretion of the investigator. In the event of abnormal laboratory findings, including but not limited to tests that may indicate abnormal liver function, repeat or additional laboratory testing may be required outside a scheduled clinic visit.

[c] Patients that do not treat a migraine with study drug for any reason during the study should attend an EoS visit to return unused study drug and the eDiary. No other assessments are required.

[d] Phone call after attack 1 or after 1 month of treatment, whichever comes first.

[e] Adapted for the assessment of the ideation and behavior categories only (the Intensity of Ideation and Lethality of Behavior sections are removed).

[f] Required if triggered by the Self-Harm Supplement Form per instructions.

3. Introduction

3.1. Study Rationale

Pivotal trials of acute treatments for migraine should address both the efficacy in single migraine attacks and the consistency of the therapeutic response over multiple attacks. In 2 Phase 3 single migraine attack studies, lasmiditan demonstrated statistically significant superiority versus placebo in the proportion of patients who were headache pain-free at 2 hours postdose as well as the proportion of patients who were free of their migraine-associated most bothersome symptoms (MBS) at 2 hours postdose.

This global, multicenter, placebo-controlled, double-blind study will assess the efficacy, consistency of response, and safety of lasmiditan in acute treatment of 4 migraine attacks with or without aura. The primary hypotheses of the study are that lasmiditan is superior to placebo as measured by the proportion of participants who have pain freedom at 2 hours postdose during the first attack, and that lasmiditan shows consistency of effect as defined by pain freedom at 2 hours in at least 2 out of 3 attacks.

3.2. Background

Migraine is a common neurological disorder and was ranked by the World Health Organization (WHO) in their 2010 Global Burden of Disease survey as 1 of 7 most debilitating conditions, and as the third most common disease in the world among both males and females (Steiner et al. 2013). Migraine prevalence was estimated to be 11.6% (Woldeamanuel and Cowan, 2017). Regional crude migraine prevalence was 16.4% in Central and South America, 11.4% in Europe, 10.4% in Africa, 10.1% in Asia, and 9.7% in North America.

Although the introduction of triptans improved the acute treatment of migraine, some patients still lack adequate treatment. A recent analysis of the American Migraine Prevalence and Prevention study concluded that 40% of patients with episodic migraine have significant unmet needs; the most frequent complaints were headache-related disability (19%) and dissatisfaction with current medications (15%) (Buse et al. 2012).

Treatment of patients with migraine and known cardiovascular (CV) disease or CV risk factors is particularly challenging because the incidence of myocardial infarction, stroke, claudication, diabetes, hypertension, and hypercholesterolemia are all higher in individuals with migraine compared with the general population (Bigal et al. 2010; Adelborg et al. 2018). While triptans are often used as first-line therapy, not all patients with migraine respond to or tolerate triptans. In addition, concerns about CV safety are believed to limit the prescription of triptans in some patients with migraine in the United States (Dodick et al. 2004). Hence, there is a significant unmet need for novel migraine therapies with a distinct mechanism of action from that of triptans.

Other therapies including nonsteroidal anti-inflammatory drugs, opioids, and barbiturates are not specifically targeted to treat migraine and have limitations. Nonsteroidal anti-inflammatory drugs have limited effectiveness and some side effects including labeled warnings concerning

CV risk. Opioids and barbiturates also have limited efficacy and carry well known risks including overuse, dependency, and adverse effects. For these reasons, there is substantial unmet medical need for new medications for acute treatment of migraine (Lipton et al. 2013; Tfelt-Hansen & Diener 2012).

Lasmiditan is a high-affinity, centrally-penetrant, highly selective 5-hydroxytryptamine (5-HT [serotonin]) 1F receptor agonist without significant pharmacological activity at 5-HT1B or 5-HT1D receptors. It has a chemical structure and pharmacologic profile that is distinct from the triptans, the current standard of care for acute migraine treatment, which were developed for their vasoconstrictor properties (Humphrey et al. 1990; Goadsby 2009; Mitsikostas and Tfelt-Hansen 2012). Evidence suggests that lasmiditan exerts its therapeutic effects in the treatment of migraine by decreasing neuropeptide release and inhibiting pain pathways including the trigeminal nerve (Labastida-Ramírez et al. 2017) without causing vasoconstriction in human coronary arteries (Ramadan et al. 2003).

Two Phase 3 multicenter, double-blind, placebo-controlled lasmiditan studies, including LAHJ with 100-mg and 200-mg dose arms and LAHK with 50-mg, 100-mg, and 200-mg dose arms to treat a single migraine attack have been completed (Lilly 2018 [IB]). The primary endpoint in each study was the proportion of patients who were headache pain-free at 2 hours postdose (defined as mild, moderate, or severe headache pain reduced to none). In both studies, this endpoint was significant for all doses of lasmiditan versus placebo. The key secondary endpoint was the proportion of patients who were free of their migraine-associated MBS at 2 hours postdose (defined as the associated symptom present and identified as MBS prior to dosing and then absent at 2 hours). In both studies, this endpoint was significant for all doses of lasmiditan versus placebo.

Study LAHL (an open-label, 12-month safety study of lasmiditan (100 mg and 200 mg) in the acute treatment of migraine) is a Phase 3, prospective, randomized study in adults with migraine. Patients who completed either Study LAHJ or Study LAHK were given the opportunity to enroll in Study LAHL, which is designed to assess the safety and tolerability of long-term intermittent use of lasmiditan 100 mg and lasmiditan 200 mg for the acute treatment of migraine. Study LAHL was initiated on 13 November 2015 and is currently ongoing.

Lasmiditan is generally well tolerated. In the Phase 3 studies, a treatment-emergent adverse event (TEAE) was defined as an event that first occurred or worsened in severity after baseline and within 48 hours of a first or second dose (if applicable) of study drug. The most common TEAEs reported in Study LAHJ/301 and Study LAHK/302 were dizziness, paresthesia, somnolence, fatigue, and nausea. A majority of the TEAEs were mild or moderate in severity and self-limiting in nature.

Trials to assess the consistency of response are recommended by the International Headache Society (IHS 2012) and by the European Medicines Agency (EMA 2007). Also, in studies of patients with migraine, consistency of response is one of the most important attributes of migraine medications (Lipton et al. 2005).

3.3. Benefit/Risk Assessment

Lasmiditan has been shown to be effective for the treatment of acute migraine with or without aura in adults. In Phase 3 trials, lasmiditan showed statistically significant superiority over placebo on the primary endpoints including pain freedom and MBS freedom at 2 hours after taking study drug. Lasmiditan was generally well tolerated with the most common TEAEs including dizziness, paresthesia, somnolence, fatigue, and nausea. Generally, these TEAEs were mild or moderate in severity and self-limiting. All doses of lasmiditan were associated with driving impairment in a study of healthy volunteers on a computer-based driving simulator. Patients should restrict their driving, operation of heavy machinery, or other similar activities after taking study drug as described in the informed consent form (ICF). Based on the statistically significant and clinically relevant effects of lasmiditan for treatment of acute migraine in adults with identified safety issues only including generally mild-to-moderate and transient tolerability issues, the positive benefit to risk profile of lasmiditan supports the conduct of this study to further evaluate and understand the efficacy, consistency, and safety of lasmiditan across 4 migraine attacks.

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

4. Objectives and Endpoints

Table LAIJ.4.1 shows the objectives and endpoints of the study.

Table LAIJ.4.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on migraine headache pain freedom compared to placebo	• The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack
• To evaluate the consistency of response to lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 2 out of 3 attacks
Secondary	
Efficacy	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on freedom from MBS compared to placebo	• The proportion of patients in each group that are free of MBS associated with migraine at 2 hours postdose during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on pain relief compared to placebo	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on sustained freedom from pain compared to placebo	• The proportion of patients in each group with 24-hour and with 48-hour sustained pain freedom during the first attack defined as pain-free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication
• To evaluate the need for rescue medication in patients treated with lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group requiring rescue medication for migraine within 24 hours of treatment during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg at 2 hours on freedom from symptoms associated with migraine compared to placebo	• The proportion of patients in each group that are free of symptoms associated with migraine at 2 hours postdose during the first attack, including each of the following: phonophobia, photophobia, nausea, and vomiting
• To assess the probability of migraine relapse in patients treated with lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group with migraine recurrence at 24 and 48 hours during the first attack defined as return of any headache in patients who were pain-free at 2 hours
• To explore the time course of lasmiditan 200 mg and 100 mg efficacy compared to placebo	• The proportion of patients in each group at each time point with pain freedom, pain relief, freedom from MBS, and no disability postdose during first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on migraine-related disability compared to placebo	• Mean change from baseline in total score and individual items as measured by the MIDAS scale, in each group at end of study
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on disability during migraine attacks compared to placebo	• The proportion of patients in each group with no disability as measured by the disability item, at 2 hours postdose during the first attack

Objectives	Endpoints
Secondary, *Efficacy*, continued	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on PGIC compared to placebo	• The proportion of patients in each group very much or much better as measured by PGIC, at 2 hours postdose during the first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on HRQoL during an acute migraine attack compared to placebo	• Mean HRQoL score for domains of social functioning, migraine symptoms, and feelings/concerns, as measured by the 24-hour MQoLQ, in each group at 24 hours postdose during first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on treatment satisfaction compared to control	• The proportion of patients in each group who are satisfied with their treatment at EoS as measured by a 4-item questionnaire
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg on health utility compared to placebo	• Mean change from baseline in utility in each group as measured by the EQ-5D-5L, at 24 hours postdose during first attack
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg in triptan nonresponders	• The proportions of patients in the subpopulation of triptan nonresponders that achieve primary and secondary objectives in each group during the first attack • The proportions of patients in the subpopulation of triptan nonresponders versus other patients that achieve primary and secondary objectives in each group during the first attack
Consistency	
• To evaluate the consistency of lasmiditan 200 mg and 100 mg on migraine headache pain relief in 2 out of 3 attacks compared to placebo	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose in at least 2 out of 3 attacks
• To evaluate the consistency of response to lasmiditan 200 mg and 100 mg in 3 out of 4 attacks compared to control	• The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 3 out of 4 attacks
• To evaluate the consistency of lasmiditan 200 mg and 100 mg on migraine headache pain relief in 3 out of 4 attacks compared to control	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose in at least 3 out of 4 attacks
• To evaluate the consistency of lasmiditan 200 mg and 100 mg in triptan nonresponders	• The proportions of patients in the subpopulation of triptan nonresponders versus other patients that achieve consistency in each group defined as pain freedom during 2 out of 3 attacks
Exploratory	
• To evaluate in females the efficacy, as measured by migraine pain and associated symptoms, of lasmiditan compared to placebo on migraine attacks occurring in proximity to menses	• During a 5-day window starting 2 days before the onset of menstruation, the proportion of migraine attacks in menstruating females with migraine pain freedom, pain relief, and MBS freedom at 2 hours after dosing in each group
• To evaluate the efficacy of lasmiditan on total migraine freedom	• Proportion of patients in each group who have total migraine freedom, defined as no pain and no migraine-associated symptoms, at 2 hours postdose during the first attack

Objectives	Endpoints
Exploratory, continued	
• To explore the effect of lasmiditan on the consistency of 2-hour freedom from MBS during 2 out of 3 attacks	• The proportion of patients in each group that are free of MBS associated with migraine at 2 hours postdose during 2 out of 3 attacks
• To evaluate the efficacy of lasmiditan on HRQoL with respect to domains of work functioning and energy/vitality during an acute migraine attack	• Mean HRQoL score for domains of work functioning and energy/vitality, as measured by the 24-hour MQoLQ, in each group at 24 hours postdose during first attack
• To evaluate the efficacy of lasmiditan on HCRU	• Mean change from baseline in HCRU in each group
• To evaluate the efficacy of lasmiditan 50 mg	• The proportions of patients with pain freedom, pain relief, MBS freedom, no disability, and very much or much better as measured by PGIC, at 2 hours postdose in patients treated with lasmiditan 50 mg during attacks 3 and 4 versus placebo during attacks 3 and 4
• To explore the efficacy of lasmiditan on time to meaningful relief and the time to pain freedom	• The time to meaningful relief and time to pain freedom in each group during each attack

Abbreviations: 24-hour MQoLQ = 24-Hour Migraine Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-dimension 5-level scale; HCRU = Health Care Resource Utilization; HRQoL = Health-Related Quality of Life; MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment Test; PGIC = Patient Global Impression of Change.

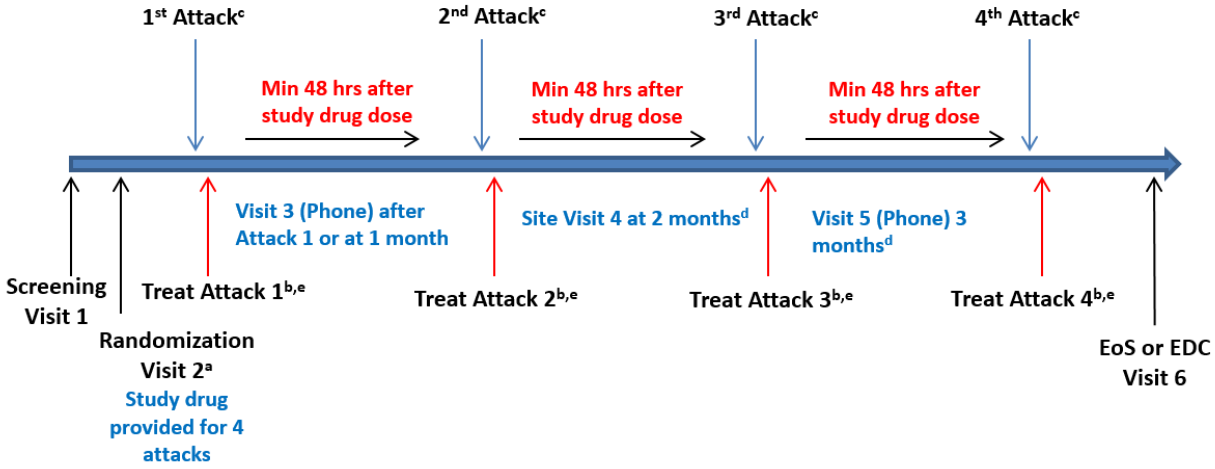
5. Study Design

5.1. Overall Design

Study H8H-MC-LAIJ is a prospective, multicenter, randomized, double-blind, modified parallel, placebo-controlled Phase 3 study of adult patients suffering from migraine with or without aura. Patients will have a history of migraine for at least 1 year, 3 to 8 migraine attacks per month, and disabling migraine as defined by a Migraine Disability Assessment Test (MIDAS) score ≥11. The treatment group sequences are summarized in Table LAIJ.5.1 and will include 1 treatment group that receives lasmiditan 200 mg for 4 attacks, 1 treatment group that receives lasmiditan 100 mg for 4 attacks, and a control group that receives placebo for 3 attacks and lasmiditan 50 mg for 1 attack. The control group will consist of 2 treatment sequence groups (1:1) where 1 group will receive lasmiditan for attack 3 and the other group will receive lasmiditan for attack 4.

Patients will be asked to treat 4 migraine attacks with study drug on an outpatient basis. Patients will be provided with doses for treatment of all 4 attacks. Each patient's study participation will consist of a screening visit (Visit 1) followed by a randomization visit (Visit 2) 3-to-30 days after screening, a Treatment Period of up to 16 weeks including phone visits and 1 site visit, and an end-of-study visit (EoS) at least 7 days after treating the last migraine attack (or at 4 months ±2 weeks after Visit 2).

Figure LAIJ.5.1 illustrates the patient flow design.



Abbreviations: EDC = early discontinuation; EoS = end of study; hrs = hours; min = minimum.

[a] Preventive treatment allowed (if stable 3 months prior to V1).

[b] At each attack patient will take 3 tablets to maintain blinding.

[c] Attacks treated do not need to be consecutive.

[d] Phone call/Visits will only occur if all 4 attacks are not completed by that time.

[e] Patient will wait to take study drug until migraine pain is moderate/severe; must be the FIRST treatment for the migraine taken within 4 hours of onset.

Figure LAIJ.5.1. Illustration of patient flow design for Protocol H8H-MC-LAIJ.

Table LAIJ.5.1. Treatment Group Sequences

Treatment Group Sequences	Attack 1	Attack 2	Attack 3	Attack 4
Lasmiditan 200 mg	LTN200	LTN200	LTN200	LTN200
Lasmiditan 100 mg	LTN100	LTN100	LTN100	LTN100
Control 1	placebo	placebo	LTN50	placebo
Control 2	placebo	placebo	placebo	LTN50

Abbreviations: LTN200 = lasmiditan 200 mg; LTN100 = lasmiditan 100 mg; LTN50 = lasmiditan 50 mg.

To avoid differential drop out which could bias and compromise the study, patients should not be informed about the treatment group sequences described in Table LAIJ.5.1. Instead, patients should be informed that no patient will receive placebo for all attacks.

5.1.1. Screening (Visit 1)

At the screening visit (Visit 1) patients will provide written informed consent and will be screened to review the inclusion and exclusion criteria. Study eligibility will be assessed on the basis of medical history including detailed migraine history meeting the International Classification of Headache Disorders (ICHD)-3 classification 1.1 or 1.2.1 for migraine, onset of migraine prior to age 50, 3 to 8 migraine attacks per month but <15 headache days per month during the past 3 months, baseline physical examination, vital signs, clinical laboratory tests, 12-lead electrocardiogram (ECG) and responses to the MIDAS questionnaire indicating disabling

migraine. Patients will be asked about any concomitant medication use as well as any CV events in the last 6 months and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease. A Columbia-Suicide Severity Rating Scale (C-SSRS) will be completed. Patients will receive some initial introduction to the electronic diary (eDiary) and the site will assess whether the patient is willing and able to use the eDiary to record data during their migraine attacks.

See Table LAIJ.2.1 for a complete list of assessments performed at Visit 1.

For patients not meeting study requirements at the screening visit or found to not qualify based on laboratory assessments, there will be no additional site visits.

5.1.2. Randomization (Visit 2)

At Visit 2, patients will be randomly assigned treatment as described in Section 5.1, will have additional assessments (see Table LAIJ.2.1), will be dispensed study drug, and will begin the Treatment Period. If available and where local regulations and ethical review boards (ERBs) allow, patients will also watch a training video designed to address patient expectations with regard to participation in a placebo-controlled trial and the difference between medical treatment and research. The patient will receive detailed instruction on the use of the eDiary and on dosing their migraine attacks with study drug.

5.1.3. Treatment Period

During the treatment period, patients will participate in phone visits after attack 1 or at 1 month (whichever comes first) and at 3 months of study participation, and a site visit at 2 months of study participation. Patients completing their 4 migraine attacks sooner than these time points will move directly to their EoS visit.

For each of 4 attacks, patients will be instructed to treat their migraine within 4 hours of onset providing that the headache severity is at least moderate or severe at the time, is not improving, and no other migraine treatment has been taken. Patients will record their response to study drug over the next 48 hours using the eDiary set up to remind the patient to complete assessments at specific postdose time points: 0.5, 1, 2, 4, 6, 24, and 48 hours. There must be at least a 48-hour gap after taking study drug for the treated attack, before treating the next migraine with study drug.

For migraine attacks which do not meet the criteria above or when the patient is unable to treat with study drug and complete all study procedures during a particular migraine, they may use their usual migraine medication for that migraine and then treat the next appropriate migraine with study drug. In summary, patients are requested to treat 4 consecutive appropriate migraine attacks with study drug, but this is not required if it is not possible.

As described in detail in Section 7.2.1, patients requiring medication for rescue or for migraine recurrence may take their own unexcluded medication.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Patients

Approximately 2100 patients will be screened to achieve approximately 1600 patients randomized, approximately 1150 patients with data for first attack, and approximately 800 patients with data for consistency assessment. An additional 200 patients may be randomized if there is an insufficient number of patients with complete data for consistency assessment.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure for the last visit for the last patient.

5.4. Scientific Rationale for Study Design

The patient population for this study will closely align to the study population studied in the lasmiditan Phase 3 program to date.

A modified parallel design was chosen after consideration of multiple design options. The modified parallel design was previously used successfully to assess the consistency of telcagepant over 4 attacks (Ho et al. 2010). This design was chosen over a parallel placebo-controlled design because of reduced risk of unblinding leading to differential drop-out rates.

A frequently used approach, termed random-insertion-of-placebo, is for each patient to receive placebo for 1 of their attacks. However, relative to this approach, the modified parallel approach in this study has beneficial features, including the opportunity to study the consistency of response to 2 doses of lasmiditan (100 mg and 200 mg) with a relatively simple study design. Finally, while random-insertion-of-placebo provides the consistency of treatment, it does not provide an opportunity for comparing the consistency of effect in patients treated with drug versus placebo.

The efficacy of lasmiditan 100 mg and 200 mg will be assessed during the first attack by comparing the results in those groups with the results with placebo in the control group.

The number of attacks is 4 and the duration of the treatment phase of the study is up to 16 weeks. Patients with 3 to 8 migraine attacks per month will be recruited to increase the probability that patients will achieve 1 or more evaluable migraine attacks per month as recommended in the IHS guideline (IHS Clinical Trials Subcommittee 2012).

Inclusion of the control group

The inclusion of the control group provides the opportunity to compare the efficacy and consistency of response to lasmiditan 100 mg and 200 mg to placebo, improved maintenance of blinding since patients in the control group will receive lasmiditan 50 mg for 1 attack, more patient acceptability since they will not receive placebo for all attacks, and the opportunity to assess the efficacy of lasmiditan 50 mg during 1 attack. Placebo effect in acute treatment of migraine varies from 6% to 47%, highlighting the importance of comparing active study drug to placebo. Because rescue medication is permitted after 2 hours, the use of placebo in the design is ethically appropriate (Lipton et al. 2005).

5.5. Justification for Dose

Two single-attack Phase 3 studies of lasmiditan have been completed, and these studies show dose-dependent efficacy of lasmiditan versus placebo to increase freedom from both pain and MBS with lasmiditan. All doses (50 mg, 100 mg, and 200 mg) showed statistically significant superiority versus placebo on pain freedom, MBS freedom, and pain relief versus placebo. In general, the efficacy of lasmiditan was dose dependent, with lasmiditan 50 mg showing the least efficacy and lasmiditan 200 mg showing the most efficacy. Safety analysis showed TEAEs were increased with lasmiditan compared to placebo, including dizziness, paresthesia, somnolence, fatigue, nausea, and lethargy. In general, these TEAEs were observed to increase in a dose-dependent manner (ie, they were lowest with lasmiditan 50 mg and highest with lasmiditan 200 mg). These TEAEs were usually mild to moderate in severity and self-limiting. Because of the relatively greater efficacy of lasmiditan 100 mg and 200 mg, the main study arms will be lasmiditan 100 mg, lasmiditan 200 mg, and control. To further understand the effects of lasmiditan 50 mg, the control group will receive lasmiditan 50 mg for 1 attack.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Type of Patient and Disease Characteristics

[1] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age at time of screening (Visit 1) with migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 or 1.2.1 (ICHD-3; see Appendix 5)

[2] history of disabling migraine for at least 1 year

[3] migraine onset before the age of 50 years

[4] history of 3 to 8 migraine attacks per month (<15 headache days per month) during the past 3 months

[5] MIDAS score ≥11

[6] able and willing to complete an eDiary to record the details of each migraine attack treated with study drug

Patient Characteristics

[7] are men or women; if women, must agree to abide by the following guidance:

women of child-bearing potential must agree to use a highly effective method of contraception (that is, one with less than 1% failure rate) such as combination oral contraceptives, implanted/injected contraceptives, intrauterine devices, or sterile partner until 30 days after the last dose of study medication

women of child-bearing 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 (for example, calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are *not* acceptable methods of contraception

women not of child-bearing potential may participate and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
- post-menopausal – defined as either

- a woman between 40-50 years of age with an intact uterus, not on hormone therapy, who has had
  - cessation of menses for at least 1 year, and
  - a follicle-stimulating hormone >40 mIU/mL;
- a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either
  - cessation of menses for at least 1 year, or
  - at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or
- a woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
- a woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

Informed Consent

[8] are able and willing to give signed informed consent

[9] agree not to post any personal medical data related to the study or information related to the study on any website or social media site (eg, Facebook, Twitter, LinkedIn, Google+, etc.) until the entire trial has completed

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

Medical Conditions/ Prior and Concomitant Therapy

[10] known hypersensitivity to lasmiditan, or to any excipient of lasmiditan oral tablets

[11] history or evidence of hemorrhagic stroke, epilepsy, or any other condition placing the patient at increased risk of seizures

[12] history of recurrent dizziness and/or vertigo including benign paroxysmal positional vertigo, Meniere's disease, vestibular migraine, and other vestibular disorders

[13] history of diabetes mellitus with complications (diabetic retinopathy, nephropathy, or neuropathy)

[14] history of orthostatic hypotension with syncope

[15] significant renal or hepatic impairment in the opinion of the investigator or if they meet hepatic monitoring criteria (see Section 9.4.5.1)

[16] patients who, in the investigator's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or those who have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5

(Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C–SSRS, or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within the past month of Visit 1 or 2

[17] Exclusion criterion [17] has been deleted.

[18] history, within past 12 months, of chronic migraine or other forms of primary or secondary chronic headache disorder (eg, hemicranias continua, medication overuse headache where headache frequency is ≥15 headache days per month [Appendix 5 and Appendix 6])

[19] use of more than 3 doses per month of either opioids or barbiturates

[20] initiation of or a change in concomitant medication to reduce the frequency of migraine episodes within 3 months prior to Screening/Visit 1

[21] female patients who are pregnant or breast-feeding

[22] women of child-bearing potential who test positive for pregnancy based on a serum pregnancy test collected at Visit 1

[23] history of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or currently using drugs of potential abuse or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence

[24] have a positive urine drug screen for any substances of abuse at Visit 1

Note: A retest is allowed if the urine drug screen is positive for any prescribed substance or if, in the judgment of the investigator, there is a medically acceptable explanation for the positive result. The results of the retest must be negative at or prior to Visit 2

[25] have an acute, serious or unstable medical condition, or a history or presence of any other medical illness including but not limited to any autoimmune disease, CV, hepatic, respiratory, hematological, endocrine, psychiatric, or neurological disease, or any clinically significant laboratory abnormality, that, in the judgment of the investigator, indicates a medical problem that would preclude study participation

[26] known hypersensitivity to multiple drugs

Prior/Concurrent Clinical Trial Experience

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

[28] if patient recently took an investigational product, 5 half-lives or 30 days or requirements based on local regulations (whichever is longer) should have passed

[29] have previously completed or withdrawn from this study or any other study investigating lasmiditan

Other Exclusions

[30] are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[31] are Lilly employees

Patients with test results which did not meet the inclusion/exclusion criteria may have the relevant test repeated once if it was thought to represent a laboratory error; a reversible, clinically insignificant intermittent condition; or was not consistent with the patient's historical values. If inclusion/exclusion criteria were not met after the repeat test, the patient should not be enrolled in the study.

6.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria 10 through 18, 21, 22, 25, and 26 are for excluding patients with significant illnesses or conditions that may affect their safety or confound study results. Exclusion Criteria 19 and 20 exclude patients with current or prior therapies that could negatively impact the safety of the patient or influence the analysis of the results. Exclusion Criteria 23 and 24 exclude treatments or illicit substances that may impact study results. Exclusion Criteria 27, 28, and 29 exclude patients using drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of AEs or drug interactions. Exclusion Criteria 30 and 31 prevent conflict of interest in study patients.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreening once with approval from Lilly Medical for only the criteria shown below. The interval between screening and rescreening must be at least 45 days or longer if required for the specified timeframes in the inclusion/exclusion criteria or concomitant medication list. If rescreening is performed, the individual must sign a new ICF and will be assigned a new identification number.

- Inclusion Criterion [1]: If patients are less than age 18 at time of informed consent, they may be rescreened if they reach age 18 during the study enrollment period
- Exclusion Criterion [22]: false positive pregnancy test

Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 2 may be rescreened if additional time is needed to meet the duration requirement.

7. Treatments

7.1. Treatments Administered

This study involves treatment with lasmiditan 200 mg, 100 mg, and 50 mg or placebo administered by mouth for migraine headaches of moderate to severe intensity. Table LAIJ.7.1 shows the treatment regimens.

Each dose will consist of 3 tablets for the treatment of a single migraine attack.

- lasmiditan 50-mg dose – 1 lasmiditan 50-mg tablet and 2 lasmiditan 100 mg matching placebo
- lasmiditan 100-mg dose – 1 lasmiditan 100-mg tablet, 1 lasmiditan 50 mg matching placebo, and 1 lasmiditan 100 mg matching placebo
- lasmiditan 200-mg dose – 2 lasmiditan 100-mg tablets and 1 lasmiditan 50 mg matching placebo
- placebo – 1 lasmiditan 50 mg matching placebo and 2 lasmiditan 100 mg matching placebo

Table LAIJ.7.1. Treatment Regimens

Regimen	Attack 1	Attack 2	Attack 3	Attack 4
LTN200 mg Dose Group	LTN200 mg 2×100-mg lasmiditan tablets 1×50 mg lasmiditan matching placebo	LTN200 mg 2×100-mg lasmiditan tablets 1×50 mg lasmiditan matching placebo	LTN200 mg 2×100-mg lasmiditan tablets 1×50 mg lasmiditan matching placebo	LTN200 mg 2×100-mg lasmiditan tablets 1×50 mg lasmiditan matching placebo
LTN100 mg Dose Group	LTN100 mg 1×100-mg lasmiditan tablet 1×50 mg lasmiditan matching placebo 1×100 mg lasmiditan matching placebo	LTN100 mg 1×100-mg lasmiditan tablet 1×50 mg lasmiditan matching placebo 1×100 mg lasmiditan matching placebo	LTN100 mg 1×100-mg lasmiditan tablet 1×50 mg lasmiditan matching placebo 1×100 mg lasmiditan matching placebo	LTN100 mg 1×100-mg lasmiditan tablet 1×50 mg lasmiditan matching placebo 1×100 mg lasmiditan matching placebo
Control 1	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo	LTN50 mg 1×50-mg lasmiditan tablet 2×100 mg lasmiditan matching placebo	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo
Control 2	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo	LTN50 mg 1×50-mg lasmiditan tablet 2×100 mg lasmiditan matching placebo

Abbreviations: LTN200 = lasmiditan 200 mg; LTN100 = lasmiditan 100 mg; LTN50 = lasmiditan 50 mg.

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- at the end of the study returning all unused medication to Lilly, or its designee, unless the sponsor and sites have agreed all unused medication is to be destroyed by the site, as allowed by local law

7.1.1. Packaging and Labelling

Clinical study materials will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment at Visit 2. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Patients will be randomized 1:1:1 to the lasmiditan 200-mg, lasmiditan 100-mg, and control groups.

The IWRS will be used to assign double-blind investigational product to each patient. At Visit 2, patients will be provided with sufficient study drug to treat 4 migraine attacks. Site personnel will confirm that they have located the correct investigational product by entering a confirmation number found on the investigational product into the IWRS.

To achieve between-group comparability, the randomization will be stratified by country.

7.2.1. Selection and Timing of Doses: Study Treatment and Other Migraine Treatments

Patients will be randomized 1:1:1 to the lasmiditan 200-mg, lasmiditan 100-mg, and control groups. The doses will be administered for migraine attacks of moderate to severe intensity. The actual time of all dose administrations will be recorded in the eDiary. Patients will be instructed to take 3 tablets as the FIRST treatment for a new migraine attack.

- The migraine is at least of moderate or severe severity.
- Migraine should be treated within 4 hours of onset.
- No prior analgesic or acute migraine treatment or symptom-modifying medication (for example, antiemetic) has been taken to treat the current migraine attack.
- Patients should not take study drug within 24 hours after taking triptans, ergots, opioids, and barbiturates.

Rescue or Recurrence Medication. Between 2 and 24 hours after dosing, patients may take their own unexcluded medication for rescue treatment (headache pain freedom is not achieved at 2

hours) or for treatment of recurrent headache (headache pain freedom is achieved at 2 hours but recurs after 2 hours). Patients should not take any medications until 2 hours after taking a dose of study drug and completing the 2-hour assessments. After that, they may take unexcluded alternative medications for rescue or recurrence. The investigator should advise patients of appropriate medications to be taken for rescue or recurrence, and inform patients that triptans, ergots, opioids, and barbiturates MUST NOT be taken within 24 hours of study drug administration (that is, 24 hours before or after). The use of rescue or recurrence medication should be recorded in the patient's paper journal.

7.3. Blinding

This is a double-blind study.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

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

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly clinical research physician (CRP) for the patient to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The patient's safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. 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. Dosage Modification

Dosage modification is not allowed.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for the following:

- confirming appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment

- ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with provided instructions, 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

Patient compliance with study drug will be assessed. Compliance will be assessed by direct questioning, counting returned tablets, and so on. Deviation(s) from the prescribed dosage regimen should be recorded in the case report form (CRF).

Study drug will be taken by the patient on an outpatient basis. Upon review of eligibility at Visit 2, study drug to treat all 4 attacks will be provided. Information on date and time of each dose will be recorded by patient in the eDiary. Patients will return all unused study drug to the site at the end of study visit. The site will document which tablets are returned. A patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

7.7. Concomitant Therapy

Concomitant medications (including devices) for migraine or pain prior to study enrollment and concomitant medication used to treat other medical conditions prior to study enrollment will be recorded during Screening/Visit 1.

Any changes in dosage or new medications added as a result of intercurrent illness during the patient's time on study must be recorded in the CRFs.

Use of the following medications is prohibited for the duration of a patient's participation in the study from Screening/Visit 1 through EoS:

- any investigational treatment other than lasmiditan
- if a patient requires the initiation of migraine prophylaxis (concomitant medication to reduce the frequency of migraine episodes) or a change in ongoing migraine prophylaxis after the Screening/Visit 1 they should be withdrawn from the study

7.8. Treatment after the End of the Study

7.8.1. Treatment after Study Completion

Lasmiditan will not be made available after conclusion of the study to patients because other effective therapies for migraine are available.

7.8.2. Special Treatment Considerations and Minimization of Risk

All doses of lasmiditan were associated with driving impairment in a study of healthy volunteers on a computer-based driving simulator. Patients should restrict their driving, operation of heavy machinery, or other similar activities after taking study drug as described in the ICF.

Because of the potential of lasmiditan to cause central nervous system (CNS)-related side effects (see Section 3.2 and IB), advise patients to use caution if taking study medication in combination with alcohol or other CNS depressants.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Subject Decision**
  - the patient requests to discontinue investigational product.

- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via eCRF.

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

  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
  - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
  - alkaline phosphatase (ALP) >3X ULN
  - ALP >2.5X ULN and TBL >2X ULN
  - ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

Not applicable for this as needed medication.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment and safety

follow up should be performed as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the main protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- investigator decision
    - the investigator decides that the patient should be discontinued from the study
- patient decision
    - the patient requests to discontinue study drug or to be withdrawn from the study
- patient becomes pregnant or is breastfeeding
- if a patient requires the initiation of migraine prophylaxis (concomitant medication to reduce the frequency of migraine episodes) or a change in ongoing migraine prophylaxis after the Screening/Visit 1 they should be withdrawn from the study

Discontinuation due to suicidality. It is recommended that a patient be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the patient should be discontinued from study drug if, during the study, a patient

- is, in the investigator's judgment, actively suicidal and therefore deemed to be at significant risk for suicide
- answers "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C–SSRS, or answers "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within the past month of the assessment

When a patient discontinues from a study due to suicidal ideation and/or behavior, the same follow-up procedures will be used as would be done for discontinuation due to any other AEs leading to discontinuation.

Patients discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

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

Site personnel, or an independent third party, will attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the patient will not be considered lost to follow-up.

Lilly personnel will not be involved in any attempts to collect vital status information.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities (Table LAIJ.2.1), with the study procedures and their timing (including tolerance limits for timing).

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

Unless otherwise stated in the 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

9.1.1. Primary Efficacy Assessments

Patient Diary

Patients will be introduced to the eDiary at Visit 1 and trained on the use of the eDiary at Visit 2. Efficacy data for each attack will be collected in the eDiary. Patients will record the date and time at which their migraine headache starts and when it first becomes moderate or severe. They will also record the date and time of taking study drug. Patients will be asked to assess their headache severity at specified time points: 0 (predose), 0.5, 1, 2, 4, 6, 24, and 48 hours postdose using the IHS 4-point headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain) (see Appendix 7).

9.1.2. Secondary Efficacy Assessments

Patient Diary

Secondary efficacy data will also be collected in the eDiary.

At the time points 0 (pre dose), 0.5, 1, 2, 4, 6, 24, and 48 hours, patients will assess the presence or absence (yes or no) of accompanying symptoms: photophobia, phonophobia, nausea, and vomiting. At time 0 (pre dose) patients will select from the accompanying symptoms present (from nausea, phonophobia, or photophobia only) which one is the most bothersome to them (see Appendix 7).

Patients will also be asked to record the time at which headache relief became meaningful to them and the time at which they become headache pain-free. At 2 and 24 hours after dosing with study drug, patients will be asked to record their global impression of change (PGIC) using a 7-point scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse) (see Appendix 7).

Patients should record details of AEs, concomitant medication use, and any other relevant information in the patient's paper journal and these will be reviewed at the next visit.

Recording Use of Rescue/Recurrence Medication

Between 2 and 24 hours after dosing, patients may take their own unexcluded medication for rescue treatment (headache pain freedom is not achieved at 2 hours) or for treatment of recurrent headache. The use of rescue or recurrence medication should be recorded in the patient's paper journal.

Migraine Quality of Life Questionnaire (MQoLQ): The 24-hour Migraine Quality of Life Questionnaire (24-hr MQoLQ) has been specifically developed to measure the HRQoL of patients with migraine within a 24-hour period after having taken migraine medication. The 24-hour MQoLQ is a 15-item, self-administered questionnaire. The items cover 5 domains (work functioning, social functioning, energy and vitality, feelings and concerns, and migraine symptoms) (Hartmaier et al. 1995; Santanello et al. 1995, 1997). Each domain consists of 3 questions answered on a 7-point scale where 1 indicates maximum impairment and 7 indicating no impairment. A domain score is calculated by summing the responses to the 3 questions and the domain score ranges from 3 to 21. The questionnaire will be administered 24 hours after dosing with study drug during each migraine.

MIDAS: The MIDAS is a patient-rated scale which was designed to quantify headache-related disability over a 3-month period. This instrument consists of 5 items that reflect the number of days reported as missed, or with reduced productivity at work or home and social events. Each question is answered as the number of days during the past 3 months of assessment, ranging from 0 to 90, with the total score being the summation of the 5 numeric responses. A higher value is indicative of more disability (Stewart et al. 1999, 2001). This instrument is considered reliable and valid, and is correlated with clinical judgment regarding the need for medical care (Stewart et al. 1999, 2001). For clinical interpretability, 4 categorical grades were developed based on the total score: Grade I (0 to 5) is for little or no disability, Grade II (6 to 10) is for mild disability, Grade III (11 to 20) is for moderate disability, and Grade IV (21+) is for severe disability. The severe disability category has subsequently been subdivided into Grade IV-A (severe [21 to 40]) and Grade IV-B (very severe [41 to 270]) because a high proportion of patients with chronic migraine are in Grade IV (Blumenfeld et al. 2011). Two additional questions (A and B) collect information on the frequency of headaches and the intensity of the headache pain. These are not scored in the MIDAS Questionnaire but are included to provide clinically relevant information that may aid in treatment and management decisions. The MIDAS will be captured at screening as part of the inclusion criteria and again at EoS with the recall period adjusted to capture disability since the patient enrolled in the study (depending on how quickly the patient completes the 4 migraine attacks, this could be from approximately 1 to 4 months).

mTOQ-6: The mTOQ is a validated, self-administered questionnaire that assesses the efficacy of current acute migraine treatment (Lipton et al. 2009) and is demonstrated to measure an autonomous outcome domain related to, but distinct from, functioning and HRQoL over a 4-week period (Lipton et al. 2009). The items assess the domains of functioning, rapid relief,

consistency, recurrence, and side effects (Serrano et al 2015). This study will use the 6-item version (mTOQ-6) at baseline/first visit with Likert type response options of Never (0 points); Rarely (0 points); Less than half the time (1 points); and Half the time or more (2 points). A total score from 0 to 8 is calculated by summing the points from 4 of the items (2-hour pain freedom, sustained 24-hour pain relief, comfortable to make plans, and perceived control) which define categories of acute treatment response: very poor (0), poor (1-5), moderate (6-7), and maximum (8) treatment efficacy (Lipton et al. 2015). This questionnaire will be administered at Visit 2.

EQ-5D-5L: 5-Dimensions 5-Levels (EQ-5D-5L) questionnaire is a widely used, generic questionnaire that assesses health status (The EuroQol Group 1990; Herdman et al. 2011). This is a patient-rated scale. The questionnaire consists of 2 parts. The first part assesses 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that have 5 possible levels of response (no problems, slight problems, moderate problems, severe problems, extreme problems). This part of the EQ-5D can be used to generate a health state index score, which is used to compute quality-adjusted life years for utilization in health economic analyses. The health state index score is calculated based on the responses to the 5 dimensions, providing a single value on a scale from less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than death) to 1 (perfect health), with higher scores indicating better health utility. The second part of the questionnaire consists of a visual analog scale on which the patient rates their perceived health state from 0 (the worst health you can imagine) to 100 (the best health you can imagine). The EQ-5D-5L will be captured at Visit 2 and at 0 and 24 hours postdose during each migraine.

Disability: Disability will be measured by determining the level of interference with normal activities with 4 response options including not at all; mild interference, marked interference; and need complete bed rest. This will be evaluated at 0, 0.5, 1, 2, 4, 6, and 24 hours postdose during each migraine.

Patient Global Impression of Change (PGIC): Patient global impression of change will be measured at 2 and 24 hours postdose with a 7-point scale ranging from very much better to very much worse during each migraine.

Treatment Satisfaction: Treatment satisfaction will be evaluated at the EoS visit by determining the patient's level of satisfaction (ranging from extremely dissatisfied to extremely satisfied); their willingness to take this treatment again (ranging from strongly disagree to strongly agree) and if they would they recommend this treatment to another patient (ranging from strongly disagree to strongly agree).

9.1.3. Appropriateness of Assessments

The assessments collected during this study are standard and generally recognized as reliable, accurate, and relevant. The study has 2 primary endpoints. Pain freedom at 2 hours postdose is a recommended primary endpoint to assess efficacy of a migraine treatment. Based on regulatory guidance for consistency studies, the other primary endpoint is consistency of effect.

The other assessments are also consistent with regulatory guidance and are commonly used in studies of medications for acute treatment of migraine.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients 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 patient. Such events should be recorded on the AE page of the eCRF.

The investigator is responsible for the appropriate medical care of patients 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 patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves or until the event stabilizes with appropriate diagnostic evaluation. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record the following via eCRF for each AE: time of onset, time of termination, severity, and their assessment of the potential relatedness of each AE to protocol procedure and investigational product.

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

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

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via initiation of the SAE eCRF. Once the SAE eCRF form is initiated, an email is automatically triggered to the Sponsor's global patient safety department. Investigators can contact the sponsor via telephone at any time using the qualified medical personnel or Lilly affiliate medical contact details which are provided in the site study file. If alerts are issued via telephone, they are to be immediately followed with official notification via completion of the SAE eCRF. If the eCRF is unavailable (for example, for system maintenance) for a period of time that would compromise the sites' ability to report an event within 24-hrs of awareness, a paper version of the form should be downloaded from the InvestigatorSpace portal, completed by the investigator, and submitted via fax to the Sponsor's global patient safety department. This form includes a fax cover page that is pre-populated with the appropriate fax number. Serious adverse events submitted via the paper method are entered into the eCRF once the database is available. The 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Patients with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during 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.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient 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.

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 identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, 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 studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

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

9.3. Treatment of Overdose

Refer to the IB.

9.4. Safety

The safety assessments are described below.

9.4.1. Electrocardiograms

For each patient, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2) as a baseline. There will be no central reading of ECGs.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Investigators may repeat an ECG collection as medically needed. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Vital Signs

Vital signs will include body temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in the sitting position prior to blood draws, according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.3. Laboratory Tests

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

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Other Tests

Columbia Suicide-Severity Rating Scale (C-SSRS): A scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner et al. 2011). The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience according to the Schedule of Activities (Section 2). The tool was developed by the National Institute of Mental Health (NIMH) trial group (Treatment of Adolescent Suicide Attempters Study) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

Two versions of the C-SSRS will be used:

- The screening version will be administered at Screening/Visit 1
- The "since last visit" version will be administered at Visit 2 and Visit 4 (at 2 months) and at V6 (EoS)

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form. If an adverse event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

Assessment of driving accidents/violations: In order to further evaluate the impact of lasmiditan on driving, an assessment of driving accidents/violations will be conducted by site personnel according to the Schedule of Activities (Section 2).

9.4.5. Safety Monitoring

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

9.4.5.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3X ULN, AST ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

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

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Genetics

9.7.1. Whole Blood Sample for Pharmacogenetic Research

A whole 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 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 patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits. 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 become(s) 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, and candidate gene studies. Regardless of technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

Not applicable.

9.9. Medical Resource Utilization and Health Economics

Health Care Resource Utilization and Employment Status: The Health Care Resource Utilization questionnaire (HCRU) will be solicited by study personnel while documenting patient responses. The HCRU consists of 3 questions, asking about the number of hospital emergency room visits, overnight stays in a hospital, and any other visits with a healthcare professional that occurred since the patient started in the study, outside of visits associated with their participation in the clinical trial. Patients are also specifically asked about the number of healthcare events that are related to migraine attacks. The baseline visit will include the same questions but with the past 6 months as the recall period.

A question on employment status will also be solicited according to the Schedule of Activities, given the correlation and potential confounding with health outcome measures.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 2100 patients will be screened to achieve approximately 1600 randomized, approximately 1150 with data for first attack, and approximately 800 with complete data for consistency assessment. An additional 200 patients may be randomized if there is an insufficient number of patients with complete data for consistency assessment.

Eligible patients will be randomized in blinded fashion in a 1:1:1 ratio to lasmiditan 200 mg, lasmiditan 100 mg, or control. The control group will consist of 2 treatment sequence groups where all patients receive placebo for 3 attacks and are randomized 1:1 where 1 group will receive lasmiditan 50 mg for attack 3 and the other group will receive lasmiditan 50 mg for attack 4.

Using a 1-sided, 2-sample comparison of proportions at a 1-sided alpha of 0.025, a sample size of 380 patients per treatment arm for the first attack provides >90% power to detect a difference in headache pain-free response at 2 hours for assumed true rates of 29% for lasmiditan 100 mg and 19% for placebo for the first attack. The power is expected to be higher for the comparison of lasmiditan 200 mg to placebo given the larger effect of lasmiditan 200 mg versus lasmiditan 100 mg observed in previous studies.

For the consistency primary endpoints, assuming 0.3 and 0.2 correlation coefficients among multiple attacks for lasmiditan and placebo respectively, and assuming a consistent response rate at each attack for lasmiditan and placebo, a sample size of 260 patients per treatment arm provides >90% power for 2-hour headache pain-free consistency for the 200-mg dose arm and nearly 90% power for consistency in the 100-mg dose arm.

10.2. Populations for Analyses

For purposes of analysis, the populations are defined below. For efficacy analyses, patients are evaluated by attack and by the group to which they are randomized. For safety analyses, patients will be analyzed according to the treatment group they actually received, which will generally be the same as randomized treatment unless there is an error.

Population	Description
Entered	All participants who sign informed consent
ITT	All randomized patients who use at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity asssessments at or before 2 hours postdose.
mITT	All randomized patients who use at least 1 dose of study drug for an mITT-evaluable attack, defined as a treated attack of at least moderate pain severity with any postdose pain severity assessments at or before 2 hours postdose.
ITT consistency	All randomized patients who experience a sufficient number of successes or failures (defined in Section 10.3.1) during ITT-evaluable attacks for any of the consistency analyses.
mITT consistency	All randomized patients who experience a sufficient number of successes or failures (defined in Section 10.3.1) during mITT-evaluable attacks for any of the consistency analyses .
Safety	All randomized patients who take at least 1 dose of study drug, regardless of whether or not they undergo any study assessments.

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. The statistical analysis plan (SAP) will be finalized and approved prior to unblinding of treatment at database lock.

Efficacy analyses will be conducted on the ITT population. This set includes all randomized patients who use at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity asssessments at or before 2 hours postdose. Patients will be evaluated by the attack and group to which they were randomized.

Consistency analyses will be conducted on the ITT consistency population. This set includes all randomized patients who experienced a sufficient number of successes or failures during ITT-evaluable attacks for any of the consistency analyses. The “sufficient number” is defined differently for the 2 endpoints related to consistency (that is, 2 out of 3 attacks and 3 out of 4 attacks):

- Two of 3: To evaluate the 2 out of 3 primary consistency endpoint, the results of ITT-evaluable attacks in the lasmiditan 100-mg and 200-mg groups will be assessed, and the ITT-evaluable attacks treated with placebo in the control group will be used for comparison. For patients with more than 3 ITT-evaluable attacks, only the first 3 will be considered.

  The population for the 2 out of 3 consistency endpoint with sufficient number of successes or failures is defined as all patients who experienced at least 2 successes or 2 failures during their first 2 or 3 ITT-evaluable attacks.

- Three of 4: To evaluate the 3 out of 4 consistency endpoint, all ITT-evaluable attacks will be used. For the control group, the results of all ITT-evaluable attacks treated with lasmiditan 50 mg or placebo will be included. The control group is used for comparison.

  The population for the 3 out of 4 consistency endpoint with sufficient number of successes or failures is defined as all patients who experienced at least 3 successes or 2 failures during ITT-evaluable attacks.

For analyses where mITT populations are specified, the definitions are the same as for ITT populations, except based on mITT-evaluable attacks.

Tests of the primary and gated secondary endpoints, as specified in the SAP, will be conducted at a 1-sided significance level of 0.025; tests of all other endpoints will be conducted at a 2-sided significance level of 0.05.

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

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

Patient disposition will be summarized by treatment group. Reasons for discontinuation for all patients will be tabulated for treatment groups, and comparisons between treatment groups will be assessed by Fisher's exact test.

10.3.2.2. Patient Characteristics

Patient characteristics will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous measures and for categorical measures (sample size, frequency, and percentages). Treatments will be compared by using analysis of variance techniques for continuous data and Pearson's chi-square or Fisher's exact test for categorical data.

The results of these tests will be used in a descriptive way to highlight potential imbalances between the treatment groups. Patient characteristics may include, but are not limited to: age, gender, race/ethnicity, height, weight, body mass index, and migraine history.

Patient characteristics will be summarized on all study populations.

10.3.2.3. Concomitant Therapy

Frequency and percentages will be calculated by treatment for concomitant medication. Treatments will be compared using Fisher's exact test.

10.3.2.4. Compliance

Treatment compliance will be assessed in terms of the actual dose. Treatment compliance will be used to characterize the patients and determine clinical evaluability for some analyses. Treatment compliance will be summarized within each treatment group and each attack by means of descriptive statistics (n, mean, SD, median, minimum and maximum).

Ediary compliance will be summarized within each treatment group and each attack group.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The first primary objective of this study is to assess the efficacy of lasmiditan 200 mg and lasmiditan 100 mg on migraine headache pain freedom. The primary measurement is the proportion of patients having pain freedom (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack. This analysis will be performed on the ITT population.

The second primary objective of this study is to assess the consistency of efficacy of lasmiditan 200 mg and lasmiditan 100 mg on migraine headache pain freedom. The primary measurement is the proportion of patients having pain freedom (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 2 out of 3 attacks. This analysis will be performed using the ITT consistency population.

The primary objective for the study is met if the result from at least 1 of the 4 hypothesis tests specified above (lasmiditan 200 mg or 100 mg compared with placebo on migraine headache pain freedom, lasmiditan 200 mg or 100 mg compared with placebo on consistency of efficacy) is statistically significant.

Logistic regression with categorical terms for treatment and geographic region will be used to statistically evaluate the proportions of patients achieving migraine headache pain freedom in first attack for lasmiditan treatment groups versus placebo and also in the consistency analyses comparing lasmiditan treatment groups versus placebo. In order to control for overall type I error, the primary analyses will be tested using a multiple comparisons procedure that preserves overall type I error at 1-sided alpha level of 0.025. This multiple comparisons procedure will be defined in the SAP, which contains the graphic scheme and weights for alpha propagation.

As a sensitivity analysis, the primary and gated secondary efficacy endpoints will be repeated on the mITT population. Additionally, the consistency endpoints will be repeated in the mITT consistency population.

10.3.3.2. Secondary Analyses

The secondary measures will be analyzed using the ITT and ITT consistency populations.

Logistic regression will be used to statistically evaluate the proportions of response among lasmiditan groups and placebo. The model contains categorical terms for treatment and geographic region. The comparisons will be between lasmiditan groups versus placebo at first attack and 2 out of 3 consistency endpoints. The comparisons will be between lasmiditan groups

versus control group for the 3 out of 4 attacks consistency endpoints. For continuous endpoints, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) will be used to assess the effect of lasmiditan. The raw total score or change from baseline of total score are dependent variables. The model includes fixed categorical effect of treatment and geographic region and baseline as covariate. The primary comparison will be between the lasmiditan groups versus placebo.

In order to control for overall type I error, the primary and a subset of secondary objectives will be gated as described in the SAP. The gated secondary analyses will be tested using a multiple comparisons procedure that preserves overall type I error at 1-sided alpha level of 0.025. If any of the null hypotheses are rejected for the primary endpoints, the gated secondary endpoints will be tested according to the multiple comparisons procedure defined in the SAP.

10.3.3.3. Tertiary/Exploratory Analyses

Logistic regression will be used to statistically evaluate the proportions among lasmiditan groups and placebo group for exploratory endpoints. The primary comparison will be between lasmiditan groups versus placebo at first attack and 2 out of 3 attacks.

Analysis of variance or ANCOVA will be used to assess the effect of lasmiditan over placebo or control for continuous endpoints. The model includes fixed categorical effect of treatment and geographic region and baseline as covariate.

10.3.4. Safety Analyses

10.3.4.1. Treatment-Emergent Adverse Events

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the postbaseline phase compared with the baseline phase. For each TEAE, the reported severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) will be used in the treatment-emergent computation. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (preferred term, High Level Term, or system organ class [SOC]) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level. An AE with time of onset within 48 hours after a dose of study drug, or an event that worsens in intensity within 48 hours after a dose of study drug will be considered a TEAE. An AE that occurs in the interval after 48 hours of dosing until EoS/Visit 6 will not be considered a TEAE. For events that are sex-specific, the denominator and computation of the percentage will include only patients from the specific sex.

Frequency counts and percentages will be presented for subjects with TEAEs within each SOC and preferred term, separated by treatment arm. Both subjects ever experiencing an event as well as total events will be presented. Descriptive statistics will also be calculated for each treatment arm for AE relationship and AE severity. If multiple intensities are reported for a given TEAE for a subject, the most severe intensity will be counted. Analyses will be performed by treatment groups across all attacks and for each attack. For the control arm, placebo and lasmiditan 50 mg will be evaluated separately. Other details can be found in the SAP.

10.3.4.2. Columbia-Suicide Severity Rating Scale

Suicide-related thoughts and behaviors and self-injurious behavior with no suicidal intent, based on the C-SSRS, will be listed by patient.

10.3.4.3. Vital Signs

The number and percentage of patients meeting criteria for treatment-emergent abnormalities in vital signs and weight at any time during study will be summarized by treatment group.

10.3.4.4. Labs

By-patient listings of clinical laboratory data will include indications of values that are outside the reference ranges, and values that are clinically significant. Shift tables describing out-of-reference range shifts will be provided for clinical laboratory test results from Screening/Visit 1 to EoS/Visit 6, as appropriate by treatment arm and dose.

10.3.4.5. Assessment of Driving Accidents

Assessment of accidents/violations will be listed by patient and treatment group.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Other Analyses

10.3.7.1. Health Economics

Mean HRQoL score in each group for 24-hour MQoLQ and change from baseline for MIDAS (item scores and total score), EQ-5D-5L, and the disability item will be analyzed. In addition, categorical analyses will be performed for disability and PGIC. Changes in health care resource utilization and employment status will also be evaluated. Details are summarized in the SAP.

10.3.7.2. Subgroup Analyses

Subgroup analyses for the primary efficacy and consistency endpoints and pain relief at 2 hours will include the following subgroup variables:

- age
- sex
- weight
- racial origin
- previous response to triptan
- geographical region
- cardiovascular risk factors
- migraine headaches treated more than 4 hours after onset

Additional details are available in the SAP.

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

11. References

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
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.
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CV	cardiovascular
ECG	electrocardiogram
EDC	early discontinuation

eDiary	electronic diary
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EoS	end of study
EQ-5D-5L	EuroQol 5-dimension 5-level scale
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
HCRU	Health Care Resource Utilization
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IHS	International Headache Society
Informed consent	A process by which a patient 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 patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalised ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	institutional review board
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IVRS/IWRS	interactive voice-response system/interactive web-response system

LLT	lower level term
LTN	lasmiditan
MBS	most bothersome symptom
MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment Test
mITT	modified intention to treat
MQoLQ	24-Hour Migraine Quality of Life Questionnaire
mTOQ-6	Migraine Treatment Optimization Questionnaire
PGIC	Patient Global Impression of Change
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QoL	quality of life
SAE	serious adverse event
SAP	Statistical Analysis Plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An AE with time and date of onset on or within 48 hours after a dose of study drug, or an event that worsened in intensity within 48 hours of a dose of study drug.
ULN	upper limit of normal
WOCBP	women of child-bearing potential

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a,b]	**Clinical Chemistry**[a,b]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Glucose, nonfasting
Urinalysis[a,b]	Albumin
Specific gravity	Cholesterol
pH	Creatine kinase (CK)
Protein	
Glucose	**Pregnancy Test** (females only) [c]
Ketones	Serum pregnancy
Blood	Urine pregnancy test (local)
Urine leukocyte esterase	
	Serum follicle-stimulating hormone (FSH) [c]
Urine drug screen	
	Stored Samples
	Pharmacogenetic sample (genetic sample/DNA)

Abbreviations: DNA = deoxyribonucleic acid; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Results will be confirmed by the Central Lab at the time of initial testing.

[c] Pregnancy tests to be assessed in women of child-bearing potential; FSH to be assessed as appropriate according to details in Inclusion Criterion #7.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for:

- ensuring that the patient 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 patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

The investigator or an 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, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

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

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

Appendix 3.1.5. Investigator Information

Investigators in this clinical trial should be neurologists, headache specialists, or other specialists with experience in headache clinical trials and treating migraine patients.

Appendix 3.1.6. 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.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR 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.

An investigator selected by the study team will serve as the CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

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

Appendix 3.2. 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

- sponsor start-up 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 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 patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, 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 original source documents.

Appendix 3.2.1. Data Capture System

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

In this study, patient data will be collected directly via an electronic patient-reported outcome (ePRO) eDiary as part of an ePRO/Clinical Outcome Assessment (COA) system. This will include questions on headache pain, migraine associated symptoms, dosing, and use of rescue or recurrence medication. Patient-rated scales/questionnaires will also be collected directly via the ePRO eDiary (see Appendix 7). Data entered into the ePRO/COA system will serve as the source data.

If ePRO records are stored at a third party site, investigator sites will have continuous access to the source documents during the study and will receive an archival copy at the end of the study for retention.

Any data for which the ePRO instrument record will serve to collect source data will be identified and documented by each site in that site's study file.

Electronic case report form data will be encoded and stored in a clinical trial database. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper

documentation provided by the patient will include, for example, The Migraine Disability Assessment Test, Treatment Satisfaction and Employment Status questionnaires, C-SSRS, and Driving assessment.

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

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly, 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.

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study H8H-MC-LAIJ is described in the Clinical Trial Agreement.

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Diagnostic Criteria for Selected Migraine Types

International Classification of Headache Disorders-3 Diagnosis and Diagnostic Criteria per International Headache Society 2018

1.1 Migraine without aura

Previously used terms: Common migraine; hemicranias simplex

Description: Recurrent headache disorder manifesting in attacks lasting 4–72 hours Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

A. At least five attacks fulfilling criteria B–D

B. Headache attacks lasting 4–72 hours (when untreated or unsuccessfully treated)

C. Headache has at least two of the following four characteristics:

1. unilateral location

2. pulsating quality

3. moderate or severe pain intensity

4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:

1. nausea and/or vomiting

2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis

1.2 Migraine with aura

Previously used terms: Classic or classical migraine; ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine; migraine accompagnée; complicated migraine

Description: Recurrent attacks, lasting minutes, of unilateralfully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C

B. One or more of the following fully reversible aura symptoms:

1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least three of the following six characteristics:

1. at least one aura symptom spreads gradually over ≥5 minutes
2. two or more aura symptoms occur in succession
3. each individual aura symptom lasts 5–60 minutes
4. at least one aura symptom is unilateral
5. at least one aura symptom is positive
6. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis

1.2.1 Migraine with typical aura

Description: Migraine with aura, in which aura consists of visual and/or sensory and/or speech/language symptoms, but no motor weakness, and is characterized by gradual development, duration of each symptom no longer than 1 hour, a mix of positive and negative features and complete reversibility

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2 Migraine with aura and criterion B below

B. Aura with both of the following:

1. fully reversible visual, sensory and/or speech/language symptoms
2. no motor, brainstem or retinal symptoms.

1.2.1.1 Typical aura with headache

Description: Migraine with typical aura in which aura is accompanied or followed within 60 minutes by headache with or without migraine characteristics.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.1 Migraine with typical aura and criterion B below

B. Headache, with or without migraine characteristics, accompanies or follows the aura within 60 minutes.

1.2.1.2 Typical aura without headache

Description: Migraine with typical aura in which aura is neither accompanied nor followed by headache of any sort.

Diagnostic criteria:

A. Attacks fulfilling criteria for 1.2.1 Migraine with typical aura and criterion B below

B. No headache accompanies or follows the aura within 60 minutes.

1.3 Chronic migraine

Description: Headache occurring on ≥15 or more days/month for more than three months, which, on at least eight days/month, has the features of migraine headache.

Diagnostic criteria:

A. Headache (migraine-like or tension-type-like) on 15 days/month for >3 months, and fulfilling criteria B and C

B. Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 Migraine without aura and/or criteria B and C for 1.2 Migraine with aura

C. On ≥8 days/month for >3 months, fulfilling any of the following:

1. criteria C and D for 1.1 Migraine without aura

2. criteria B and C for 1.2 Migraine with aura

3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative

D. Not better accounted for by another ICHD-3 diagnosis

The reason for singling out 1.3 Chronic migraine from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).

Appendix 6. Medication Overuse Headache Diagnostic Criteria

International Classification of Headache Disorders-3 Diagnosis and Diagnostic Criteria per International Headache Society 2018:

[A] Headache occurring on ≥15 days/month in a patient with a pre-existing headache disorder

[B] Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache (see notes 1 to 3 below)

[C] Not better accounted for by another ICHD-3 diagnosis.

Notes:

[1] Patients should be coded for one or more subtypes of 8.2 *Medication-overuse headache* according to the specific medication(s) overused and the criteria for each below. For example, a patient who fulfils the criteria for 8.2.2 *Triptan-overuse headache* and the criteria for one of the subforms of 8.2.3 *Non-opioid analgesic-overuse headache* should receive both these codes. The exception occurs when patients overuse combination-analgesic medications, who are coded 8.2.5 *Combination-analgesic-overuse headache* and not according to each constituent of the combination-analgesic medication.

[2] Patients who use multiple drugs for acute or symptomatic treatment of headache may do so in a manner that constitutes overuse even though no individual drug or class of drug is overused; such patients should be coded 8.2.6 *Medication-overuse headache attributed to multiple drug classes not individually overused*.

[3] Patients who are clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of their names and/or quantities are coded 8.2.7 *Medication-overuse headache attributed to unspecified or unverified overuse of multiple drug classes* until better information is available. In almost all cases, this necessitates diary follow-up.

Appendix 7. eDiary Assessments

eDiary Assessment for all attacks treated with study drug	**0h**	**0.5h**	**1h**	**2h**	**4h**	**6h**	**24h**	**48h**
Headache severity (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain)	X	X	X	X	X	X	X	X
Presence or absence (yes or no) of accompanying symptoms: photophobia, phonophobia, nausea, and vomiting	X	X	X	X	X	X	X	X
Select from the accompanying symptoms present (nausea, phonophobia or photophobia only) which one is the most bothersome	X							
Time at which headache relief became meaningful					X			
Time at which they become headache pain-free					X			
MQoLQ							X	
EQ-5D-5L	X						X	
Disability	X	X	X	X	X	X	X	
PGIC				X			X	

Abbreviations: eDiary = electronic diary; EQ-5D-5L = EuroQol 5 Dimension 5 Level; h = hours; MQoLQ = 24-Hour Migraine Quality of Life Questionnaire; PGIC = Patient Global Impression of Change.

Appendix 8. Protocol Amendment H8H-MC-LAIJ(b) Summary

Overview

Protocol H8H-MC-LAIJ (Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks [CENTURION]) has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are summarized in the following bullets and in more detail in the subsequent table:

- Updated protocol title to include the name "CENTURION."
- Modified description of endpoints associated with analyses of first attack for the subpopulation of triptan nonresponders in objectives section.
- Clarified information about C-SSRS, specifically noting that a short form of the scale is being used and clarifying administration of the self-harm supplement and self-harm follow-up forms in the Schedule of Activities.
- Clarified that driving assessments are conducted by site personnel.
- Clarified that repeat laboratory testing outside a scheduled visit may be conducted in the event of abnormal laboratory findings.
- Updated names and definitions of analysis populations for consistency with statistical analysis plan approved before first patient visit (ITT populations) or for consistency with studies this study may be compared with (mITT populations). Updated related descriptions of analyses for clarity.
- In addition, some minor points were clarified throughout, and grammatical errors and typographical errors were corrected.

Amendment Summary for Protocol H8H-MC-LAIJ Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Title Page, and Section 1, Synopsis, Title of Study	CENTURION added to protocol title.	Added to provide easy study identification for publications.
Section 1, Synopsis, Objectives/Endpoints (and Section 4, Objectives and Endpoints)	Modified description of endpoints associated with analyses of first attack for the subpopulation of triptan nonresponders.	To align with gating strategy described in statistical analysis plan.
Section 1, Synopsis, Statistical Analysis subsection	Definition of ITT population was updated.	Aligned with Version 1 of statistical analysis plan, which was approved before first-patient-visit.
	Description of consistency analyses was updated.	Clarified.
Section 2, Schedule of Activities	Rows/footnotes added regarding C-SSRS	Updated to align with recommendations of Lilly Psychobehavioral Working Group; no changes to actual procedure.
	Note about additional lab testing occurring outside scheduled visits added to footnote b.	Added to make existing procedure more apparent to sites.
Section 6.2, Exclusion Criteria	In exclusion [18], added cross-reference to Appendix 6.	Added so that cross-references to both applicable appendices were included.
Section 9.4.4, Other Tests	Added text to specify use of shortened version of the C-SSRS.	Updated to align with recommendations of Lilly Psychobehavioral Working Group; no changes to actual procedure.
	Added text to indicate that driving assessments are conducted by site personnel.	Clarified existing procedures.
Section 10.2, Populations for Analysis	Updated names and definitions of analysis populations; added mITT consistency population.	Updated for consistency with statistical analysis plan approved before first patient visit (ITT populations); or with studies this study may be compared with (mITT populations).
Section 10.3.1, General Statistical Considerations	Updated descriptions of efficacy populations, particularly definition of sufficient attacks to be included in consistency analyses.	Updated for clarity and for consistency with changes in Section 10.2
Section 10.3.3.1, Primary Analyses	Simplified description of sensitivity analyses by deleting population definition. Added analysis of consistency endpoints in mITT consistency population.	Modified to meet submission needs.

Amendment Summary, continued

Section # and Name	Description of Change	Brief Rationale
Section 10.3.3.1, Primary Analyses Section 10.3.3.2, Secondary Analyses Section 10.3.3.3, Tertiary/Exploratory Analyses	Clarified that geographic region will be included in analysis models (not country).	Aligned with statistical analysis plan.
Appendix 1, Abbreviations	Updated TEAE definition to note that treatment-emergent is limited to the 48 hours after dosing.	Updated for consistency with statistical analyis plan.
Appendix 6, Medication Overuse Headache Diagnostic Criteria	Added source for criteria.	Clarification; no change to criteria.

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underscore.

For most sections, only the sentences or paragraphs with deletions or additions have been included; ellipses may be used to take the place of material that did not change.

Title page, title

Protocol H8H-MC-LAIJ(a~~a~~b)
Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks (CENTURION)

1. Synopsis, Title of Study

Protocol H8H-MC-LAIJ Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks (CENTURION)

1. Synopsis, Objectives/Endpoints

Only rows with additions or deletions are included below.

Objectives	Endpoints
Secondary	
Efficacy	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg in triptan nonresponders	• The proportions of patients in the subpopulation of triptan nonresponders that achieve primary and secondary objectives in each group during the first attack • The proportions of patients in the subpopulation of triptan nonresponders versus other patients that achieve primary and secondary objectives in each group during the first attack

1. Synopsis, Statistical Analysis

Efficacy analyses will be conducted on the intent-to-treat (ITT) ~~efficacy~~ population. This set includes all randomized patients who use~~d~~ at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity assessments at or before 2 hours postdose ~~and had any postdose efficacy assessments~~. The primary efficacy analysis will compare the proportion of patients with 2-hour pain freedom during the first attack in the lasmiditan 200-mg group with placebo and compare the proportions of patients with 2-hour pain freedom during the first attack in the lasmiditan 100-mg group with placebo.

The consistency analyses will be conducted on the ITT consistency population, a subset of the ITT population with sufficient evaluable attacks. ~~This set includes all randomized patients who experienced 2 successes or 2 failures on 2-hour pain freedom, regardless of whether or not they had data for all attacks.~~ To evaluate the ~~2 out of 3~~ primary consistency endpoint, the proportions of patients with 2-hour pain freedom during 2 out of the first 3 evaluable attacks in the lasmiditan 200-mg and 100-mg groups will be compared to the results of the evaluable attacks treated with placebo in the control group~~s~~. ~~An attack will be defined as evaluable if there is non-missing information on 2-hour pain freedom.~~

2. Schedule of Activities

Only rows with additions or deletions are included below.

Table LAIJ.2.1. Schedule of Activities

	Visit 1[a] Screening	Visit 2 Baseline (at site)	Treatment Attack 1-4[b] All attacks: Mod/sev within 4 hrs of onset Attack 2: ≥48 hrs after dosing Attack 1 Attack 3: ≥48 hrs after dosing Attack 2 Attack 4: ≥48 hrs after dosing Attack 3			Visit 6 EoS (at site) or EDC[c]	Notes
		V1+3-30 days (pending lab results)	Visit 3 Phone Call 1 after Attack 1 or at 1 mo[d]±1 wk after V2	Visit 4 Site Visit at +2 mos±1 wk after V2	Visit 5 Phone Call 2 at 3 mos±1 wk after V2	≥7 days after last treated attack (=last dose) OR at 4 mos±2 wks after V2	
C-SSRS - BL/screening version[e]	X						
C-SSRS - since last visit version[e]		X		X		X	
Self-Harm Supplement Form	X	X		X		X	
Self-Harm Follow-up Form[f]	X	X		X		X	

[b] Attacks treated do not need to be consecutive. Minimum amount of time between attacks is 48 hours (determined by timing of dosing, i.e., the next attack may not be treated with study drug within 48 hours of taking study drug). During the treatment period, unscheduled visits may be completed at the discretion of the investigator. In the event of abnormal laboratory findings, including but not limited to tests that may indicate abnormal liver function, repeat or additional laboratory testing may be required outside a scheduled clinic visit.

[e] Adapted for the assessment of the ideation and behavior categories only (the Intensity of Ideation and Lethality of Behavior sections are removed).

[f] Required if triggered by the Self-Harm Supplement Form per instructions.

4. Objectives and Endpoints

Only rows with additions or deletions are included below.

Objectives	Endpoints
Secondary	
Efficacy	
• To evaluate the efficacy of lasmiditan 200 mg and 100 mg in triptan nonresponders	• The proportions of patients in the subpopulation of triptan nonresponders that achieve primary and secondary objectives in each group during the first attack • The proportions of patients in the subpopulation of triptan nonresponders versus other patients that achieve primary and secondary objectives in each group during the first attack

6.2. Exclusion Criteria

[18] history, within past 12 months, of chronic migraine or other forms of primary or secondary chronic headache disorder (eg, hemicranias continua, medication overuse headache where headache frequency is ≥15 headache days per month [Appendix 5 and Appendix 6])

9.4.4 Other Tests

Columbia Suicide-Severity Rating Scale (C-SSRS): A scale that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period (Posner et al. 2011). The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior occurred. The C-SSRS is administered by an appropriately trained healthcare professional with at least 1 year of patient care/clinical experience according to the Schedule of Activities (Section 2). The tool was developed by the National Institute of Mental Health (NIMH) trial group (Treatment of Adolescent Suicide Attempters Study) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

Two versions of the C-SSRS will be used:

- The screening version will be administered at Screening/Visit 1
- The "since last visit" version will be administered at Visit 2 and Visit 4 (at 2 months) and at V6 (EoS)

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

The nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form. If an adverse event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to

discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

Assessment of driving accidents/violations: In order to further evaluate the impact of lasmiditan on driving, ~~patients will be asked to respond to questions related to motor vehicle accidents and moving violations~~ an assessment of driving accidents/violations will be conducted by site personnel according to the Schedule of Activities (Section 2).

10.2. Populations for Analyses

Population	Description
Entered ~~Enrolled~~	All participants who sign informed consent
ITT ~~efficacy~~	All randomized patients who use at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity asssessments at or before 2 hours postdose ~~and have any postdose efficacy assessments~~.
mITT ~~efficacy~~	All randomized patients who use at least 1 dose of study drug for an mITT-evaluable attack, defined as a treated attack of at least moderate pain severity with any postdose pain severity assessments at or before 2 hours postdose ~~to treat a migraine within 4 hours of migraine onset and have any postdose efficacy assessments~~.
ITT consistency	All randomized patients who experience a sufficient number of successes or failures (defined in Section 10.3.1) during ITT-evaluable attacks for any of the consistency analyses ~~participants from ITT efficacy population with sufficient information on consistency of 2-hour headache pain freedom as defined in Section 10.3.1.~~
mITT consistency	All randomized patients who experience a sufficient number of successes or failures (defined in Section 10.3.1) during mITT-evaluable attacks for any of the consistency analyses.
Safety	All randomized patients who take at least 1 dose of study drug, regardless of whether or not they undergo any study assessments.

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. The statistical analysis plan (SAP) will be finalized and approved prior to unblinding of treatment at database lock.

Efficacy analyses will be conducted on the ITT ~~efficacy~~ population. This set includes all randomized patients who use~~d~~ at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity asssessments at or before 2 hours postdose~~and had any postdose efficacy assessments~~. Patients will be evaluated by the attack and group to which they were randomized.

Consistency analyses will be conducted on the ITT consistency population. This set includes all randomized patients who experienced a sufficient number of successes or failures during ITT-evaluable attacks for any of the consistency analyses. The "sufficient number" is defined differently for the ~~There are~~ 2 endpoints related to consistency (~~ie~~that is, 2 out of 3 attacks and 3 out of 4 attacks)~~.~~:

- Two of 3: To evaluate the 2 out of 3 primary consistency endpoint, the results of ~~the first 3~~ ITT-evaluable attacks in the lasmiditan 100-mg and 200-mg groups will be assessed, and the ITT-evaluable attacks treated with placebo in the control group will be used for comparison. For patients with more than 3 ITT-evaluable attacks, only the first 3 will be considered. ~~An attack is defined as evaluable if there is non-missing pain data at baseline and at 2 hours.~~

  The population for the 2 out of 3 consistency endpoint with sufficient number of successes or failures is defined as all patients who experienced at least ~~either~~ 2 successes

or 2 failures during their first 2 or 3 ITT-evaluable attacks~~, regardless of whether or not they had data for all attacks. Attacks treated with placebo are used for comparison.~~

- Three of 4: To evaluate the 3 out of 4 consistency endpoint, all ITT-evaluable attacks will be used. For the control group, the results of all ITT-evaluable attacks treated with lasmiditan 50 mg or placebo will be included. The control group is used for comparison.

  The population for the 3 out of 4 consistency endpoint with sufficient number of successes or failures is defined as all patients who experienced at least ~~either~~ 3 successes or 2 failures during ITT-evaluable attacks~~, regardless of whether or not they had data for all attacks. For the control group, the results of all evaluable attacks treated with lasmiditan 50 mg or placebo will be included. The control group is used for comparison.~~

For analyses where mITT populations are specified, the definitions are the same as for ITT populations, except based on mITT-evaluable attacks.

…

10.3.3.1. Primary Analyses

The first primary objective of this study is to assess the efficacy of lasmiditan 200 mg and lasmiditan 100 mg on migraine headache pain freedom. The primary measurement is the proportion of patients having pain freedom (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack. This analysis will be performed on the ITT ~~efficacy~~ population.

…

Logistic regression with categorical terms for treatment and ~~either country or~~ geographic region will be used to statistically evaluate the proportions of patients achieving migraine headache pain freedom in first attack for lasmiditan treatment groups versus placebo and also in the consistency analyses comparing lasmiditan treatment groups versus placebo. In order to control for overall type I error, the primary analyses will be tested using a multiple comparisons procedure that preserves overall type I error at 1-sided alpha level of 0.025. This multiple comparisons procedure will be defined in the SAP, which contains the graphic scheme and weights for alpha propagation.

As a sensitivity analysis, the primary and gated secondary efficacy endpoints ~~along with the MBS analysis~~ will be repeated on the mITT population~~ which includes those patients who treat a migraine with study drug within 4 hours of migraine onset and have any postbaseline efficacy data~~. Additionally, the consistency endpoints will be repeated in the mITT consistency population.

10.3.3.2. Secondary Analyses

The secondary measures will be analyzed using the ITT~~ efficacy~~ and ITT consistency populations.

Logistic regression will be used to statistically evaluate the proportions of response among lasmiditan groups and placebo. The model contains categorical terms for treatment and~~, country or~~ geographic region. The comparisons will be between lasmiditan groups versus placebo at first attack and 2 out of 3 consistency endpoints. The comparisons will be between lasmiditan groups versus control group for the 3 out of 4 attacks consistency endpoints. For continuous endpoints, analysis of variance (ANOVA) or analysis of covariance (ANCOVA) will be used to assess the effect of lasmiditan. The raw total score or change from baseline of total score are dependent variables. The model includes fixed categorical effect of treatment and geographic region ~~country~~ and baseline as covariate. The primary comparison will be between the lasmiditan groups versus placebo.

…

10.3.3.3. Tertiary/Exploratory Analyses

…

Analysis of variance or ANCOVA will be used to assess the effect of lasmiditan over placebo or control for continuous endpoints. The model includes fixed categorical effect of treatment and geographic region ~~country~~ and baseline as covariate.

Appendix 1. Abbreviations and Definitions

TEAE	Treatment-emergent adverse event: An AE with time and date of onset on or within 48 hours after a dose of study drug, or an event that worsened in intensity within 48 hours of a dose of study drug.~~An 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.~~

Appendix 6. Medication Overuse Headache Diagnostic Criteria

International Classification of Headache Disorders-3 Diagnosis and Diagnostic Criteria per International Headache Society 2018~~Diagnostic criteria~~:

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