LAIH Protocol (a)

Randomized, Double-blind, Placebo Controlled Trial of Lasmiditan in a Single Migraine Attack in Japanese Patients Suffering from Migraine With or Without Aura – the MONONOFU Study

NCT03962738

Approval Date: 06-Mar-2019

Protocol H8H-JE-LAIH(a) RandoMized, DOuble-bliNd, PlacebO-coNtrolled Trial Of Lasmiditan in a Single Migraine Attack in Japanese Patients SuFfering from Migraine With or WithoUt Aura – the MONONOFU study

Lasmiditan (LY573144)

Eli Lilly Japan K.K.
Kobe, 651-0086, Japan

Protocol Electronically Signed and Approved by Lilly: 07 February 2019
Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 06-Mar-2019 GMT

Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Figures

Figure **Page**

List of Appendices

Appendix **Page**

1. Synopsis

Title of Study:
Protocol H8H-JE-LAIH RandoMized, DOuble-bliNd, PlacebO-coNtrolled Trial Of Lasmiditan in a Single Migraine Attack in Japanese patients SuFfering from Migraine With or WithoUt Aura – the MONONOFU sutdy

Rationale:
In 2 Phase 3, randomized, double-blind, single migraine attack studies (Study COL MIG-301/H8H-CD-LAHJ [Study 301/LAHJ, SAMURAI] and Study COL MIG-302/H8H-CD-LAHK [Study 302/LAHK, SPARTAN]), lasmiditan (Study 301/LAHJ: 100 mg and 200 mg, Study 302/LAHK: 50 mg, 100 mg, and 200 mg) 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 symptom (MBS) (as identified by the patient from the associated symptoms of nausea, phonophobia or photophobia) at 2 hours postdose.

Lasmiditan in Japan is currently being developed for patients with migraine based on the bridging strategy described in the Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH-E5). Influences of ethnic factors on lasmiditan were evaluated in the Phase 1 Study H8H-JE-LAIE (Study LAIE), which explored the safety, tolerability and pharmacokinetics (PK) of lasmiditan in healthy Japanese and Caucasian subjects. The safety and PK results from this study, as well as the results from previous global clinical pharmacology studies, suggest that lasmiditan is unlikely to be affected by intrinsic ethnic factors and support the bridging strategy.

Study H8H-JE-LAIH (LAIH) will be conducted as the bridging trial to the Phase 3 Study 302/LAHK, with dose-response in efficacy of lasmiditan in the range of 50-200 mg. Study LAIH will assess the efficacy and safety of lasmiditan in acute treatment of a migraine attack in Japanese adult patients with or without aura.

Objectives/Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of lasmiditan 200 mg on migraine headache pain freedom compared to placebo	• The proportion of patients in each group who are pain free (defined as moderate or severe headache pain becoming none) at 2 hours postdose during the attack
Key Secondary	
• To evaluate the dose response of lasmiditan 200 mg, 100 mg, and 50 mg on migraine headache pain freedom compared to placebo	• The proportion of patients in each group who are pain free at 2 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 100 mg on migraine headache pain relief compared to	• The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none) in each group at 2 hours postdose during the attack

placebo	
Other Secondary	
• To evaluate the efficacy of lasmiditan 100 mg and 50 mg on migraine headache pain freedom compared to placebo	• The proportion of patients in each group who are pain free at 2 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on freedom from MBS compared to placebo	• The proportion of patients in each group who are free of MBS associated with migraine at 2 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, and 50 mg on pain relief compared to placebo	• The proportion of patients with pain relief in each group at 2 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on sustained freedom from pain compared to placebo	• The proportion of patients in each group with 24-hour and 48-hour sustained pain freedom during the attack defined as pain free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 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 attack, including each of the following: phonophobia, photophobia, nausea, and vomiting
• To explore the time course of lasmiditan 200 mg, 100 mg, and 50 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 after taking the dose of study drug during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 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 attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on health utility compared to placebo	• Mean change from baseline in utility in each group as measured by the EuroQol 5 dimension 5-level scale (EQ-5D-5L), at 24 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 50 mg, and 100 mg on Patient Global Impression of Change (PGI-C) compared to placebo	• The proportion of patients in each group very much or much better as measured by PGI-C, at 2 and 24 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on Health-Related Quality of Life (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 Migraine Quality of Life Questionnaire (MQoLQ), in each group at 24 hours postdose

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 = the most bothersome symptom as identified by the individual from the associated symptoms of nausea, phonophobia or photophobia; PGI-C = Patient Global Impression of Change; HRQoL = Health-Related Quality of Life.

Summary of Study Design:

Study LAIH is a prospective, multicenter, randomized, double-blind, placebo-controlled Phase 2 study of Japanese adult patients suffering from migraine with or without aura.

Summary of Treatment Arms and Duration:

Each patient's study participation will consist of a screening visit (Visit 1) followed by a randomization visit (Visit 2) 7 to 30 days after screening, a treatment period of up to 8 weeks and an end of study (EoS) visit (Visit 3) 3 to 28 days after treating the migraine attack (or at 8 weeks [+2 weeks as visit allowance] after Visit 2).

Patients will be asked to treat a migraine attack with study drug on an outpatient basis. Patients will be provided with doses for treatment of the attack at Visit 2; placebo, lasmiditan 50 mg, 100 mg, or 200 mg will be assigned. Table LAIH.1 shows the treatment group assignments for Study LAIH.

To achieve between-group comparability, the randomization will be stratified (yes or no) for current use of concomitant medication(s) that reduce the frequency of migraine episodes.

Table LAIH.1. Treatment Groups

Treatment Groups	Treatment Dose
1	Placebo
2	Lasmiditan 50 mg
3	Lasmiditan 100 mg
4	Lasmiditan 200 mg

Summary of Number of Patients:

Approximately 1157 patients will be screened to achieve approximately 880 patients randomized, and approximately 624 patients with data for a migraine attack.

Summary of Statistical Analysis:

The following statistical tests [T1] (primary), [T2] (key secondary), and [T3] (key secondary) will be conducted sequentially ([T1], [T2], then [T3]) by a gatekeeping method. This guarantees that the overall type 1 error across the set of primary and key secondary hypothesis tests is 0.05. Other assessments will not be part of the gatekeeping procedure.

- [T1] Primary: placebo vs. lasmiditan 200 mg (pain free at 2 hours) will be based on logistic regression.
- [T2] Key secondary: dose response of placebo, lasmiditan 50 mg, 100 mg, and 200 mg (pain free at 2 hours) will be based on the Cochran-Armitage trend test.
- [T3] Key secondary: placebo vs. lasmiditan 100 mg (pain relief at 2 hours) will be based on logistic regression.

The analysis population for [T1], [T2], and [T3] under the gatekeeping procedure is the modified intent-to-treat (mITT) population. This set includes all randomized patients who took at least 1 dose of study drug within 4 hours of onset of the migraine attack and have any postdose efficacy assessments.

For [T1], [T2], or [T3], if an analysis ([T1] or [T2] or [T3]) is not statistically significant, then all subsequent analyses will be conducted but will be designated as exploratory rather than confirmatory.

For the [T1] analysis, the statistical test will be based on placebo vs. lasmiditan 200 mg using the logistic regression model that includes treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and baseline usage of medications to reduce the migraine (Yes/No).

For the [T2] analysis, the Cochran-Armitage trend test will be based on placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg. The trend parameter is (0, 50, 100, and 200).

For the [T3] analysis, the statistical test will be based on placebo vs. lasmiditan 100 mg using the logistic regression model that includes treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and baseline usage of medications to reduce the migraine (Yes/No).

2. Schedule of Activities

Table LAIH.2. Schedule of Activities

Procedure	Visit 1[a] Screening	Visit 2 Baseline	Treatment period[b] Treat moderate/severe migraine attack within 4 hrs of pain onset	Visit 3 EoS or EDC[c]	Note
		+7~30 days after V1	8 weeks	3~28 days after treatment OR At 8 weeks after V2[d]	
Obtain informed consent	X				
Inclusion and exclusion criteria	X				
Demographics	X				Demographics will include age and sex.
Physical examination	X			X	
Diagnosis of migraine	X				Document migraine characteristics per IHS (ICHD-2) criteria.
Vital signs	X			X	Vital signs will include temperature, blood pressure, and pulse. Blood pressure and pulse will be measured in the sitting position prior to blood draws and dosing. Blood pressure: use local site blood pressure equipment.
Weight	X			X	
Height	X				
Employment status		X			
Complete MIDAS	X				
Complete mTOQ-6		X			
Review migraine history including prior treatment	X				Timing of onset, frequency of migraine headache, existence of aura, and prior therapy for migraine will be collected.
Review medical history and concomitant medications	X				Medical history (including risk factors for CVD and family history of CVD) will be collected.
Adverse events		X		X	
Concomitant medications		X		X	
Menstrual cycle status		X		X	Female patients will be asked the beginning date and the end date of their menstrual period at V2 and V3.

Procedure	Visit 1[a] Screening	Visit 2 Baseline	Treatment period[b] Treat moderate/severe migraine attack within 4 hrs of pain onset	Visit 3 EoS or EDC[c]	Note
		+7~30 days after V1	8 weeks	3~28 days after treatment OR At 8 weeks after V2[d]	
Neurological examination	X			X	
12-lead ECG	X			X	The ECG should be collected prior to blood draws. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
Clinical laboratory (hematology, serum chemistry, urinalysis)[e]	X			X	The hepatic algorithm will be triggered in cases of hepatic abnormalities identified by laboratory testing.
Serum pregnancy test or FSH	X			X	Pregnancy tests assessed in WOCBP; FSH assessed as appropriate only at V1 (details in Inclusion Criteria [8] in Section 6.2)
Alcohol abuse/dependence and smoking status	X				
Urine drug screen	X				Can be repeated once if the result is positive.
Pharmacogenetic sample (genetic sample/DNA)	X				
C-SSRS - baseline/screening version/ SHSF, SHFU	X				A SHFU form will be completed where applicable.
C-SSRS - since last visit version/SHSF, SHFU		X		X	A SHFU form will be completed where applicable.
Confirm eligibility		X			
Patient training video		X			
Randomization		X			
Dispense study drug		X			
Introduce eDiary including assess patient capability to use eDiary	X				
Provide study eDiary and provide detailed instructions and complete EQ-5D-5L		X			

Procedure	Visit 1[a] Screening	Visit 2 Baseline	Treatment period[b] Treat moderate/severe migraine attack within 4 hrs of pain onset	Visit 3 EoS or EDC[c]	Note
		+7~30 days after V1	8 weeks	3~28 days after treatment OR At 8 weeks after V2[d]	
Migraine attack (eDiary) documentation by patient			X		Patients will enter data into the eDiary at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4 and 24 and 48 hours after dosing. Details are described in Appendix 5. In addition to entering data during migraine attacks, patients will be reminded daily to record any adverse events and any new concomitant medication(s) during the treatment period.
Provide study paper diary and detailed instructions		X			
Documentation of adverse events and concomitant medication (paper diary)			X		
Documentation of non-study rescue/recurrence medication (paper diary)			X		
Document menstrual cycle status (paper diary)			X		
Assessment of driving accidents/violations		X		X	
Determine compliance study drug				X	
Collect unused/empty study drug pack, eDiary, and paper diary				X	

Abbreviations: C-SSRS = Columbia Suicide Severity Rating Scale; CVD = cardiovascular disease; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EDC = early discontinuation; eDiary = electronic diary; EoS = end of study; EQ-5D-5L = EuroQol 5 Dimension 5 Level; FHS = follicle stimulating hormone; ICHD-2 = International Classification of Headache Disorders 2nd Edition; IHS = International Headache Society; MIDAS = Migraine Disability Assessment Test; mTOQ6 = Migraine Treatment Optimization Questionnaire; SHSF = self-harm supplement form; SHFU = self-harm follow-up form; V = visit; WOCBP = women of child-bearing potential.

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

[b] During the treatment period, unscheduled visits may be completed at the discretion of the investigator.

[c] Patients who 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. Adverse events and use of concomitant medications must be assessed, however no other assessments are required.

[d] Patients who do not treat a migraine with study drug should attend this visit at 8 weeks after V2. Visit 3 should be finished by 8 weeks (+14 days as visit allowance) after V2.

[e] Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.

3. Introduction

3.1. Study Rationale

In 2 Phase 3, randomized, double-blind, single migraine attack studies (Study COL MIG-301/H8H-CD-LAHJ [Study 301/LAHJ, SAMURAI] and Study COL MIG-302/H8H-CD-LAHK [Study 302/LAHK, SPARTAN]), lasmiditan (Study 301/LAHJ: 100 mg and 200 mg, Study 302/LAHK: 50 mg, 100 mg, and 200 mg) 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 MBS (as identified by the patient from the associated symptoms of nausea, phonophobia or photophobia) at 2 hours postdose.

Lasmiditan in Japan is currently being developed for patients with migraine based on the bridging strategy described in the Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH-E5). Influences of ethnic factors on lasmiditan were evaluated in the Phase 1 Study H8H-JE-LAIE (Study LAIE), in which a randomized, 3-period, subject- and investigator-blind, crossover design was implemented to explore the safety, tolerability, and PK of lasmiditan in healthy Japanese and Caucasian subjects. The study had 3 cohorts, 2 of which included only Japanese subjects (Cohorts 1 and 2) and 1 (Cohort 3) which included only Caucasian subjects. Subjects were enrolled into 1 of 3 cohorts. Within each cohort, subjects were randomized to a specific treatment sequence. Randomization was stratified by sex to ensure approximately an equal number of male and female subjects in each cohort and treatment sequence. Subjects received single oral doses of 400 mg, 2 × 200 mg (repeated single doses, 2 hours apart), 200 mg, 100 mg, 50 mg lasmiditan, placebo, or 2 × placebo (repeated single doses, 2 hours apart) (Japanese subjects, Cohorts 1 and 2), or 200 mg, 100 mg, 50 mg, or placebo (Caucasian subjects, Cohort 3) on Day 1 of each period, according to their assigned treatment sequence. There was a washout period of approximately 72 hours between dose administrations across periods.

Overall, a total of 27 healthy subjects, consisting of 16 Japanese subjects (8 male and 8 female), and 11 Caucasian subjects (6 male and 5 female), between the ages of 29 and 63 years, and 24 and 64 years, respectively, participated in Study LAIE. Of the 27 subjects who entered the study, 27 were randomly assigned to treatment and received at least 1 dose of study drug. Twenty six subjects completed the study, and 1 did not complete the study (withdrew due to a family emergency).

Safety data in Japanese and Caucasian subjects from Study LAIE showed that no deaths, or serious or severe adverse events (AEs) occurred during the study. There were no discontinuations due to AEs. The most frequent treatment-emergent adverse events (TEAEs) (all causalities) reported during the study were somnolence, dizziness, and hypoaesthesia in decreasing order in the overall population of Japanese and Caucasian subjects combined. In the Integrated Safety Summary (ISS), a summary of TEAEs in non-Japanese healthy subjects (556 healthy subjects, non-elderly, 79% White) who were administered with single doses of lasmiditan over a range of 0.1 mg to 400 mg, the most frequent TEAEs reported were dizziness, somnolence, fatigue, headache, paraesthesia, and nausea in decreasing order. The TEAEs and

their frequency reported in Japanese subjects in Study LAIE are generally similar to those in the ISS. Taken together, these data suggest that there are no major differences in safety and tolerability in Japanese and non-Japanese healthy subjects. The frequency of TEAEs in Study LAIE did not differ between sexes in Japanese subjects, whereas a higher frequency of TEAEs were observed in Caucasian females. No clinically significant effect of lasmiditan on systolic blood pressure, diastolic blood pressure, or QTc interval was observed during Study LAIE across the doses investigated.

The PK data from Study LAIE appeared to be similar in Japanese and Caucasian subjects with median maximum concentration between 1.50 and 2.50 hours, and mean $t_{1/2}$ value approximately 4 hours for all dose levels and across populations. No consistent difference in the PK of lasmiditan and its metabolites was noted between male and female subjects within Japanese and Caucasian populations.

Overall, the safety and PK results in Japanese and Caucasian healthy subjects in Study LAIE and the ISS, indicate that lasmiditan is unlikely to be affected by intrinsic ethnic factors, thus supporting the conclusion that the bridging strategy can be employed for the development of lasmiditan in Japan.

The current study (H8H-JE-LAIH [LAIH]) will be conducted as the bridging trial to the Phase 3 Study 302/LAHK with dose response in efficacy in the range of 50-200 mg. Study LAIH will assess the efficacy and safety of lasmiditan in acute treatment of a single migraine attack in Japanese adult patients with or without aura.

3.2. Background

Migraine is a serious, chronic, disabling neurological disease characterized by attacks of moderate to severe headache pain associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. According to an epidemiological study conducted in Japan using the Japanese version of the International Classification of Headache Disorders (ICHD), the overall prevalence of migraine in Japan was 8.4% with a gender ratio (women/men) of approximately 3.6 (Sakai and Igarashi 1997). The prevalence of migraine was as high as 17.6% and 18.4% for women in their 30s and 40s, respectively (Takeshima et al. 2004). The World Health Organization (WHO) reports migraine on its own to be the sixth highest cause worldwide of years lost due to disability, and headache disorders collectively to be third highest, with a large social loss due to the high proportion of sufferers at labor-productivity age (WHO, 2016). In Japan, 25.8% of patients with aura of migraine and 19.5% of patients without aura of migraine answered, "I have experience of being absent from work due to headache" (Takeshima et al. 2004).

Pharmacologic approaches to the treatment of migraine include drugs to treat migraine attacks as they arise (acute treatment), and drugs to reduce the frequency of migraine attacks (preventive treatment). Acute treatment is primarily based on the following five options: acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), ergotamine, triptans, and antiemetics. Acetaminophen and NSAIDs are typically used for mild attacks while triptans are typically used for moderate to severe attacks. Antiemetics are used if patients experience nausea during

attacks. If migraine attacks are frequent or refractory, opioids, barbiturates, analgesic anesthetics, or corticosteroids are used, although they are off-label. These treatment options follow the International Headache Society (IHS) guidelines both in Japan and the United States/European Union (US/EU), and there are currently no major differences in the use of acute or preventive treatments among these regions despite differences in insurance coverage and approval status (JHS 2013).

An analysis of the American Migraine Prevalence and Prevention study found that 40.7% of patients with migraine had ≥1 significant unmet needs. Among the patients with unmet needs, 47.0% had moderate or severe headache-related disability, 37.4% were dissatisfied with their acute migraine treatment, 32.0% had excessive opioid or barbiturate use and/or probable dependence, 26.2% had a history of cardiovascular events (a group which should not take triptans or ergotamines), and 5.7% reported ≥2 visits in the preceding year to the emergency or emergent care for headache (Lipton et al. 2013). Collectively this information further highlights a need for new approaches for the acute treatment of migraine attacks that may improve the management of some patients with migraine leading to improved outcomes.

Lasmiditan, chemical name: 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4 carbonyl)pyridine-2-yl]benzamide hemisuccinate, is a high affinity, highly selective 5-HT_{1F} receptor agonist that has a >470 fold selectivity for the human 5-HT_{1F} receptor relative to the 5-HT_{1B} receptor. It has a chemical structure and pharmacologic profile that is distinct from the triptans, the current standard of care for acute treatment of migraine attacks. Lasmiditan does not contain the indole group observed in all triptans and instead has a pyridinoyl piperidine scaffold, which is unique among antimigraine medications. 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 . 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 at baseline 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, long-term 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 to have been 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. CCI [redacted]

Lasmiditan is generally well tolerated. In the Phase 3 studies, a 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 for the 100 mg and 200 mg treatment groups were: dizziness (15.4% to 17.2%); paresthesia (5.8% to 7.2%); somnolence (5.1% to 6.0%); fatigue (4.1% to 4.0%) and nausea (3.2% to 3.9%). The majority of the TEAEs were mild or moderate in severity and self-limiting with a short duration.

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 for the primary endpoints including pain freedom and MBS freedom at 2 hours after taking study drug. Lasmiditan was generally well tolerated with TEAEs >2% in any lasmiditan group including dizziness, paresthesia, somnolence, fatigue and nausea. Generally, these TEAEs were mild or moderate in severity and self-limiting with a short duration. All doses of lasmiditan were associated with driving impairment in a study of healthy volunteers based 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 the treatment of acute migraine in adults with identified safety issues only including generally mild-to-moderate tolerability issues which are self-limiting with a short duration, the positive benefit to risk profile of lasmiditan supports the conduct of this study to further evaluate and understand the efficacy and safety of lasmiditan across a single migraine attack.

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

4. Objectives and Endpoints

Table LAIH.3 shows the objectives and endpoints of the study.

Table LAIH.3. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the efficacy of lasmiditan 200 mg on migraine headache pain freedom compared to placebo in Japanese adult patients suffering from migraine with or without aura.	The proportion of patients in each group who are pain free (defined as moderate or severe headache pain becoming none) at 2 hours postdose during the attack.
Key Secondary	
• To evaluate the dose response of lasmiditan 200 mg, 100 mg, and 50 mg on migraine headache pain freedom compared to placebo • To evaluate the efficacy of lasmiditan 100 mg on migraine headache pain relief compared to placebo	• The proportion of patients in each group who are pain free at 2 hours postdose during the attack • The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none) in each group at 2 hours postdose during the attack
Other Secondary	
• To evaluate the efficacy of lasmiditan 100 mg and 50 mg on migraine headache pain freedom compared to placebo • To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on freedom from MBS compared to placebo • To evaluate the efficacy of lasmiditan 200 mg and 50 mg on pain relief compared to placebo • To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on sustained freedom from pain compared to placebo • To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg at 2 hours on freedom from symptoms associated with migraine compared to placebo • To explore the time course of lasmiditan 200 mg, 100 mg, and 50 mg efficacy compared to placebo	• The proportion of patients in each group who are pain free at 2 hours postdose during the attack • The proportion of patients in each group who are free of MBS associated with migraine at 2 hours postdose during the attack • The proportion of patients with pain relief in each group at 2 hours postdose during the attack • The proportion of patients in each group with 24-hour and 48-hour sustained pain freedom during the attack defined as pain free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication • The proportion of patients in each group that are free of symptoms associated with migraine at 2 hours postdose during the attack, including each of the following: phonophobia, photophobia, nausea, and vomiting • The proportion of patients in each group at each time point with pain freedom, pain relief, freedom from MBS, and no disability after taking the dose of study drug during the attack

Objectives and Endpoints

• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 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 attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on health utility compared to placebo	• Mean change from baseline in utility in each group as measured by the EuroQol 5 dimension 5-level scale (EQ-5D-5L), at 24 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 50 mg, and 100 mg on Patient Global Impression of Change (PGI-C) compared to placebo	• The proportion of patients in each group very much or much better as measured by PGI-C, at 2 and 24 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on Health-Related Quality of Life (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 Migraine Quality of Life Questionnaire (MQoLQ), in each group at 24 hours postdose of study during the attack

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 = the most bothersome symptom as identified by the individual from the associated symptoms of nausea, phonophobia or photophobia; PGI-C = Patient Global Impression of Change; HRQoL = Health-Related Quality of Life; MQoLQ = Migraine Quality of Life Questionnaire.

5. Overall Design

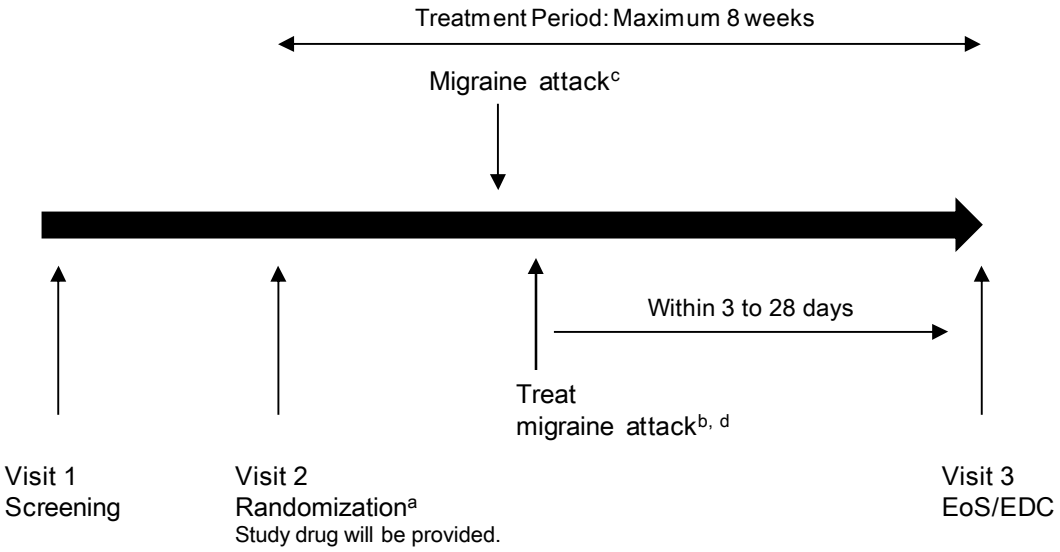
5.1. Overall Design

Study LAIH is a prospective, multicenter, randomized, double-blind, placebo-controlled Phase 2 study of Japanese 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. Patients will be asked to treat a single migraine attack with study drug on an outpatient basis. At Visit 2, patients will be provided with doses for treatment of an attack; placebo, lasmiditan 50 mg, 100 mg, or 200 mg will be assigned.

Table LAIH.1 shows the treatment group assignments for this study.

Each patient's study participation will consist of a screening visit (Visit 1), followed by a randomization visit (Visit 2) 7 to 30 days after screening, a treatment period of up to 8 weeks, and an EoS visit (Visit 3) 3 to 28 days after treating the migraine attack (or at 8 weeks [+2 weeks as visit allowance] after Visit 2). If a migraine attack is treated, the EoS visit must occur no later than 28 days following treatment of the migraine attack. Sites will encourage patients to visit as early as possible following treatment of the migraine attack.

Figure LAIH.1 illustrates the study design.



Abbreviations: EDC = early discontinuation; EoS = end of study.

a Preventive treatment allowed (if stable 3 months prior to Visit 1).

b Patients will take 3 tablets to maintain blinding.

c Patients 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 pain onset.

d Patients who do not treat a migraine with study drug should attend Visit 3 at 8 weeks after Visit 2. Visit 3 should be finished by 8 weeks (+14 days as visit allowance) after Visit 2.

Figure LAIH.1. Patient flow overview Clinical Protocol H8H-JE-LAIH.

Study governance considerations are described in detail in Appendix 3.

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 ICHD classification 2nd edition 1.1 (migraine without aura) or 1.2.1 (migraine with aura) for migraine, onset of migraine prior to age 50 years, 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 moderately to severely disabling migraine. 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 attack.

See Section 2 for a complete list of assessments performed at Visit 1.

Patients not meeting study requirements at the screening visit or found to not qualify based on laboratory assessments will be considered a screen failure and will not have further assessments (for re-screening, see Section 6.5).

5.1.2. Randomization (Visit 2)

At Visit 2, patients will be randomly assigned treatment as described in Section 7.1, will have additional assessments (see Section 2), will be dispensed study drug, and will begin the Treatment Period. If available and where the Institutional Review Board (IRB) allows, 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 instructions on the use of the eDiary and on dosing their migraine attack with study drug.

5.1.3. Treatment Period

During the treatment period, patients will treat their migraine attack with study drug. Patients who complete the assessment for their migraine attack treated by study drug will move to their EoS visit.

Patients will be instructed to treat their migraine attack within 4 hours of pain 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 be required to record their response to the dose over the next 48 hours using the eDiary starting from prior to taking the drug (pre-dose), and at specific postdose time points of 0.5, 1, 1.5, 2, 3, 4, 24, and 48 hours.

For a migraine attack that does not meet the criteria above or when the patients are unable to treat with study drug and complete all study procedures during a particular migraine attack, they may use their usual migraine medication for that migraine attack and then treat the next appropriate migraine attack with study drug. When patients take their usual migraine medication (including antiemetic), there must be at least a 24-hour gap after taking the last dose of their usual migraine medication before treating the migraine attack with study drug. Details of migraine medication is provided in the concomitant medication/therapy list.

Patients should not take any other treatments for migraine until after completing the 2 hour assessments postdose. After that, patients requiring medication for rescue (the patient is not headache pain free at 2 hours), or for migraine recurrence (the migraine becomes pain free at 2 hours but then recurs after 2 hours), may take NSAIDs, acetaminophen, and/or antiemetic drugs with approved dosage and usage in Japan. The investigator should advise patients of appropriate medications to be taken for rescue and recurrence, and that triptans, ergots, opioids, and barbiturates MUST NOT be taken within 24 hours of study drug administration. The use of any rescue and recurrence medication other than study drug will be recorded in the patient's paper diary. The total time for recording response to study drug is 48 hours.

5.2. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last visit for the last patient. Patients who 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. Adverse events and use of concomitant medications need to be assessed,

however, no other assessments are required for patients who do not treat a migraine with study drug.

5.3. Scientific Rationale for Study Design

Study LAIH is conducted as the bridging trial to Study 302/LAHK with dose response efficacy in the range of lasmiditan 50 to 200 mg. The primary endpoint is the superiority of lasmiditan 200 mg compared with placebo on pain freedom at 2 hours postdose. The key secondary endpoints are 1) to assess for dose-dependent efficacy of lasmiditan 50 to 200 mg on pain free at 2 hours postdose and 2) to evaluate the efficacy of lasmiditan 100 mg compared with placebo on pain relief at 2 hours postdose. Pain relief is an indicator of efficacy confirmed by a statistically significant difference between placebo and lasmiditan 100 mg in Study 302/LAHK and Study 301/LAHJ. Pain relief has been widely used as the primary endpoint in randomized clinical studies of acute treatment of migraine, including triptans, and has also been established as the primary endpoint in Study COL MIG-202/H8H-CD-LAHO (Study 202/LAHO).

Accordingly, a sample size as large as Study 302/LAHK is not required for Study LAIH. For Study LAIH, a sample size of approximately 880 randomized patients is sufficient, as described in Section 10.1.1.

CCI [redacted]

5.4. Justification for Dose

Three doses (lasmiditan 50 mg, 100 mg, and 200 mg) used in the Study 302/LAHK (study for bridging reference), have been selected in this Study LAIH in Japanese patients with migraine. Two single-attack Phase 3 studies (Study 301/LAHJ and Study 302/LAHK) of lasmiditan have been completed, and these studies show dose-dependent efficacy of lasmiditan versus placebo to increase freedom from headache pain 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. 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, with the most common AEs being dizziness, paresthesia, somnolence, fatigue, and nausea. In general, these TEAEs were observed to increase in a dose-dependent manner (i.e., they were lowest with lasmiditan 50 mg and highest with lasmiditan 200 mg). These TEAEs were usually mild to moderate in severity with a median duration of 1 to 5 hours.

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. Number of Patients

Approximately 1157 patients will be screened to achieve approximately 880 patients randomized, and approximately 624 patients with efficacy data for a migraine attack.

6.2. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at Visit 1:

Type of Patient and Disease Characteristics

[1] Patients with migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 and 1.2.1 (International Classification of Headache Disorders [ICHD]-2).

[2] History of disabling migraine for at least 1 year.

[3] MIDAS score ≥11.

[4] Migraine onset before the age of 50 years.

[5] History of 3 – 8 migraine attacks per month and <15 headache days per month during the past 3 months.

[6] Male or female, aged 18 years or above.

[7] Able and willing to complete an eDiary to record details of the migraine attack treated with study drug.

Patient Characteristics

[8] *Women of child-bearing potential* must agree to use a highly effective method of contraception such as combination oral contraceptives or intrauterine devices approved in Japan, or sterile partner during clinical trial period and until 30 days after the last dose of study medication and to report occurrences of pregnancy or suspected pregnancy to the investigator immediately.

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.

Male participants with pregnant female partners or female partners with child-bearing potential must agree to use a barrier method of contraception during clinical trial period and until 30 days after the last dose of study medication and to report occurrences of pregnancy or suspected pregnancy of their partner to the investigator immediately.

Informed Consent

[9] Are able and willing to give signed informed consent, and in the case of patients under 20 years old, informed consent signed by a parent or legal guardian.

[10] 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 (e.g., Facebook, Twitter, LinkedIn, etc.) until the entire trial has completed.

6.3. 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

[11] Known hypersensitivity to lasmiditan, or to any excipient of lasmiditan oral tablets.

[12] History or evidence of hemorrhagic stroke, epilepsy, or any other condition placing the patient at increased risk of seizures.

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

[14] History of diabetes mellitus with complications (diabetic retinopathy, nephropathy, or neuropathy).

[15] History of orthostatic hypotension with syncope.

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

[17] 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.

[18] Known Hepatitis B or C or HIV infection.

[19] History, within past 12 months, of chronic migraine or other forms of primary or secondary chronic headache disorder (e.g., hemicranias continua, medication overuse headache where headache frequency is ≥15 headache days per month.

[20] Use of more than 3 doses per month of either opioids or barbiturates.

[21] Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes within 3 months prior to Visit 1.

[22] Female patients who are pregnant or breast-feeding.

[23] Women who have failed to show a negative result for a serum pregnancy test collected at Visit 1.

[24] 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.

[25] 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. However, the patients who have the positive result of benzodiazepines and/or antidepressants can be allowed to stay in the trial if there is a medically acceptable explanation in the judgment of the investigator.

[26] 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, cardiovascular (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.

[27] Known hypersensitivity to multiple drugs.

Prior/Concurrent Clinical Trial Experience

[28] 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.

[29] 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.

[30] Have previously completed or withdrawn from this study or any other study investigating lasmiditan.

Other Exclusions

[31] 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.

[32] 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.

6.3.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria 11 through 19, 22, 23, 26, and 27 are for excluding patients with significant illnesses or conditions that may affect their safety or confound study results. Exclusion Criteria 20 and 21 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 24 and 25 exclude treatments or illicit substances that may impact study results. Exclusion Criteria 28, 29, and 30 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 31 and 32 prevent conflict of interest in study patients.

6.4. Lifestyle Restrictions

Not applicable.

6.5. 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 the Lilly Clinical Research Physician (CRP)/Clinical Research Scientist (CRS) for only the criteria shown below. The interval between screening and rescreening must be at least 2 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 [6]: 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 [23]: Indeterminate pregnancy test. If a patient has been reported as borderline pregnant, or if medically deemed not pregnant despite a positive pregnancy test, they may undergo a rescreening process. Patients must have a negative pregnancy test result in order to be admitted into the study.
- Exclusion Criterion [25]: For patients who have a positive urine drug screen for any substances of abuse at Visit 1, 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, a rescreening is allowed only in case a patient cannot have a retest prior to Visit 2.

Patients using a concomitant medication that requires a stable dose for a specific duration prior to Visit 1 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 50 mg, 100 mg, and 200 mg or placebo administered by mouth for a migraine headache of moderate to severe intensity.

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 LAIH.4 shows the treatment regimens.

Table LAIH.4. Treatment Regimens

Regimen	Treatment Dose
Placebo	Placebo 1×50 mg lasmiditan matching placebo 2×100 mg lasmiditan matching placebo
LY50mg Dose Group	LY50 mg 1×50 mg lasmiditan tablet 2×100 mg lasmiditan matching placebo
LY100 mg Dose Group	LY100 mg 1×100 mg lasmiditan tablet 1×50 mg lasmiditan matching placebo 1×100 mg lasmiditan matching placebo
LY200 mg Dose Group	LY200 mg 2×100 mg lasmiditan tablets 1×50 mg lasmiditan matching placebo

Abbreviations: LY200 = lasmiditan 200 mg; LY100 = lasmiditan 100 mg; LY50 = lasmiditan 50 mg.

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

- Explaining the correct use of the investigational agents 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 trial materials will be labeled according to the Japanese regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized at Visit 2.

The randomization ratio will be 7:3:7:6 to placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg.

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

To achieve between-group comparability, the randomization will be stratified (yes or no) for current use of concomitant medication(s) that reduce the frequency of migraine episodes.

At Visit 2, patients will be provided with study drug to treat a single migraine attack. 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 before patients leave the site at Visit 2.

7.2.1. Selection and Timing of Doses

The actual time of dose administration will be recorded in the patient's eDiary. Patients will be instructed to take 3 tablets as the treatment for a new migraine attack, along with the following instructions:

- The migraine must be at least of moderate or severe severity.
- The migraine must be treated within 4 hours of pain onset.
- No prior analgesic or acute migraine treatment within 24 hours of study drug administration has been taken to treat the current migraine attack.

7.2.1.1. Rescue/Recurrence Medication

Rescue medication will be permitted after completion of the 2 hour assessments if the migraine does not respond with study drug (patient is not headache pain free). If the migraine does not respond within 2 hours, a rescue dose of NSAIDs, acetaminophen, and/or antiemetic drugs may be taken after completion of the 2 hour assessments of the study drug dose. Triptans, ergots, opioids and barbiturates MUST NOT be used for rescue medication within 24 hours of study drug administration.

If the migraine responds within 2 hours (headache becomes pain free) but then recurs after 2 hours, a dose of NSAIDs, acetaminophen, and/or antiemetic drugs may be taken after completion

of the 2 hour assessments of the study drug dose. Triptans, ergots, opioids and barbiturates MUST NOT be used for recurrence medication within 24 hours of study drug administration.

The use of rescue and recurrence medication details will be recorded in the paper diary.

Figure LAIH.2 illustrates allowance period of these restricted rescue and recurrence medications.

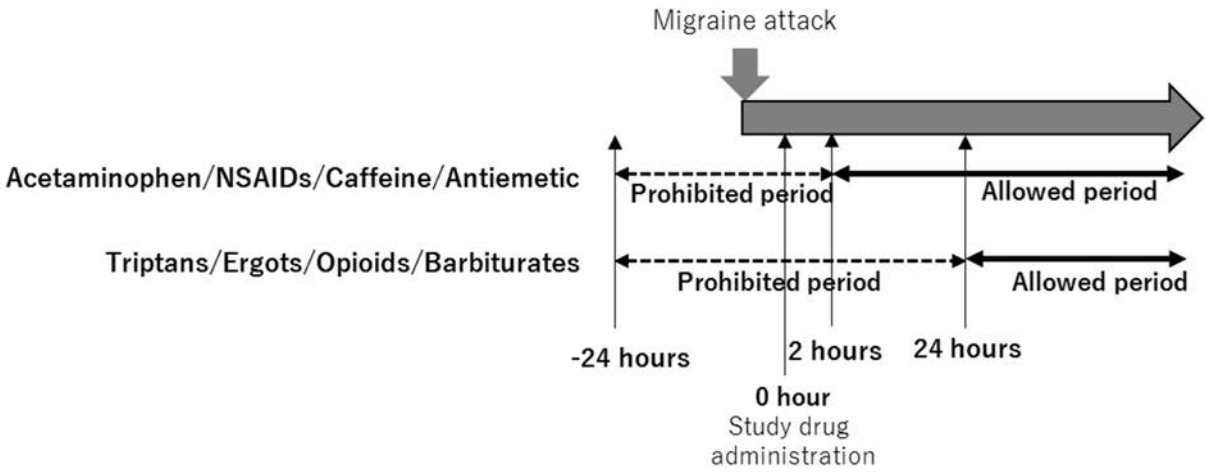


Figure LAIH.2. Allowance of restricted rescue/ recurrence medications.

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. Information regarding treatment arms will not be disclosed to investigators or patients until the final database lock.

Emergency unblinding for AEs may 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 CRP or CRS 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. Patient 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.

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 patients randomized 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 the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation and final disposition records).

7.6. Treatment Compliance

Patient compliance with study drug will be assessed. Compliance will be assessed by direct questioning, counting returned tablets, and so on. The number of returned tablets should be recorded in the case report form (CRF).

Study drug medication will be taken by the patient on an outpatient basis. Upon review of eligibility at Visit 2, study drug to treat a single migraine attack 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 EoS visit/Visit 3. The site will document which tablets are returned.

7.7. Concomitant Therapy

Concomitant medications for migraine (preventive and acute medication) or pain prior to study enrollment will be recorded during Screening/Visit 1. Concomitant medication used during a patient's participation in the study from Screening/Visit 1 through EoS/Visit 3will be recorded during Visit 2 and EoS/Visit 3.

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/Visit 3:

- 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.

Details of concomitant therapies allowed, not allowed, or restricted during the study is provided in the concomitant medication/therapy list.

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 sedation, as well as other cognitive and/or neuropsychiatric adverse reactions, lasmiditan should be used with caution if used in combination with alcohol or other central nervous system depressants.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

This is a single-dose study. If a patient discontinues prior to receiving the single dose of lasmiditan within 8 weeks of treatment period, early termination procedures will be completed per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.1.1. 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 unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- 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.
- 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 be withdrawn from the study.
- The patient becomes pregnant or is breastfeeding.
- Discontinuation due to suicidality.
    - It is recommended that the 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 adverse event 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, 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 will be collected in the eDiary. Patients will record the date and time at which their migraine headache starts. They will also record severity and the date and time of taking the study drug. Patients will be asked to assess their headache severity at specified time points: 0 (pre dose), 0.5, 1, 1.5, 2, 3, 4 and 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). The eDiary assessments are listed in Appendix 5.

9.1.2. Secondary Efficacy Assessments

Patient Diary

Other efficacy data will also be collected in the eDiary.

At the time points, 0 (pre dose), 0.5, 1, 1.5, 2, 3, 4, 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) the one that is the most bothersome to them.

Patients will also be asked to record the time of meaningful relief and the time at which they become headache pain free. At 2 and 24 hours after the study drug, patients will be asked to record their Patient Global Impression of Change (PGI-C) using a 7-point scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse). The eDiary assessments are listed in Appendix 5.

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

Recording Use of Rescue/Recurrence Medication: Refer to Section 7.2.1.1 for details.

Migraine Quality of Life Questionnaire (MQoLQ): The 24-hour Migraine Quality of Life Questionnaire (24-hr MQoLQ) has been specifically developed to measure the Health-Related Quality of Life 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 the study drug.

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 (Stewart et al. 2001). Two additional questions (A and B) collect information on the frequency of headaches and the intensity of the headache pain. These are not part of the total MIDAS score 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.

Migraine Treatment Optimization Questionnaire-6 (mTOQ-6): The mTOQ is a validated, self-administered questionnaire that assesses the efficacy of current acute migraine treatment (Lipton et al. 2009; Lipton et al. 2015). The items assess the domains of quick return to function, 2-hour pain free, sustained 24-hour pain relief, tolerability, comfortable to make plans, perceived control (Serrano et al 2015). This study will use the 6-item version (mTOQ-6) with Likert type response options of Never (1); Rarely (2); Less than half thetime (3); Half the time or more (4), producing a range of scores from 1 to 24. This questionnaire will be administered at Visit 2.

EuroQol 5-Dimension 5-Level (EQ-5D-5L): 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 of study drug.

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 (pre dose), 0.5, 1, 2, and 24 hours postdose of study drug.

PGI-C: Patient global impression of change will be measured at 2 and 24 hours postdose of study drug with a 7-point scale ranging from very much better to very much worse.

Treatment Satisfaction: Treatment satisfaction will be evaluated at 48 hours postdose of the study drug 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); if they would they recommend this treatment to another patient (ranging from strongly disagree to strongly agree) and their preference when comparing this treatment to the previous treatment ("prefer this treatment in comparison to my previous treatment" to "prefer my previous treatment in comparison to this treatment").

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 one primary endpoint. Pain freedom at 2 hours postdose is a recommended primary endpoint to assess efficacy of a migraine treatment (Tfelt-Hansen 2012). Based on regulatory guidance for this bridging study, the other assessments are also consistent with regulatory guidance and are commonly used in studies of medications for acute treatment of migraine. Pain relief has been the primary endpoint in previous migraine randomized clinical trials of acute treatment of migraine, including triptans, and has also been established as the primary endpoint in Study 202/LAHO.

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.

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, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

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 electronic case report form (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 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 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 a sponsor-approved method. 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-hours 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. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. 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 subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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 locally according to the Schedule of Activities (Section 2). There will be no central reading of ECGs.

Electrocardiograms should be collected prior to blood draws. 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 dose of the investigational 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 dose of study drug 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 dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Other Tests

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 3 (EoS).

If present, suicide ideation will be classified in 5 classes (1-5), the intensity of suicidal ideation will be classified in 5 dimensions, and any suicidal behavior will be classified in 6 classes (actual attempt, interrupted attempt, aborted attempt, preparatory acts towards and attempt, suicidal behavior, suicide).

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 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 complete a questionnaire about motor vehicle accidents and moving violations 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 alanine aminotransferase (ALT) ≥3X upper limit of normal (ULN), alkaline phosphatase (ALP) ≥2X ULN, or elevated total bilirubin level (TBL) ≥2X ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days including ALT, aspartate aminotransferase (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 via the eCRF if 1 or more of the following conditions occur:

- Elevation of serum ALT 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. Pharmacogenomics

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)/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.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 1157 patients will be screened to achieve approximately 880 patients randomized, and approximately 624 patients with data for a migraine attack.

10.1.1. Sample Size Rationale

Table LAIH.5 illustrates the power calculation.

The power calculation is based on the results of the Study 302/LAHK study. The primary endpoint (headache pain free at 2 hours postdose) results in Study 302/LAHK were 21.3%, 28.6%, 31.4%, and 38.8% for placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg, respectively, and the rates of headache pain relief at 2 hours postdose were 47.7%, 59.0%, 64.8%, and 65.0% for placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg, respectively.

To ensure sufficient total statistical power for the primary and two key secondary analyses, the number of randomized patients will be set at 880. This sample size has 85.6% power. More specifically, the study will include:

- Number of screened patients = 1157.
- Number of randomized patients = 880 (= 1157*0.76, approximately 24% screen failure based on assumptions from LAIJ), with [placebo:lasmiditan 50 mg:lasmiditan 100 mg:lasmiditan 200 mg] = 268:114:268:230 (7:3:7:6 ratio) for the attack.
- Number of patients who have an attack = 624 (= 880*0.71, approximately 29% of patients would not dose to treat a migraine attack during the 8 week period based on Study 302/LAHK/Study 301/LAHJ), with [placebo:lasmiditan 50 mg:lasmiditan 100 mg:lasmiditan 200 mg] = 190:81:190:163 (7:3:7:6 ratio).

Table LAIH.5. Study Power Calculation

	Arm	N
Arm and number of patients	PLA	190
	LY50	81
	LY100	190
	LY200	163
	Total	624
Power	Primary [T1] : PLA vs LY200 = 93.6% (2 sided, alpha = 0.05) Key secondary [T2]: CA (PLA,LY50,LY100,LY200) = 94.9% (2 sided, alpha = 0.05)	

	Key secondary [T3]: PLA vs LY100 = 91.2% (2 sided, alpha = 0.05) Total (primary and two key secondaries) = 85.6%
Primary endpoint/Key secondary endpoints	[T1] and [T2]: Pain free at 2 hours postdose [T3]: Pain relief at 2 hours postdose

Abbreviations: alpha = type 1 error; CA = Cochran Armitage trend test; LY200 = lasmiditan 200 mg; LY100 = lasmiditan 100 mg; LY50 = lasmiditan 50 mg; PLA = placebo; N = number of patients for the corresponding arms which correspond to modified ITT (mITT) population.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined. Patients in all of these populations will be evaluated by the drug to which they were randomized except the safety population (Table LAIH.6).

Table LAIH.6. Populations for Analyses

Population	Description
All enrolled population	All participants who sign informed consent
All randomized population	All randomized patients
ITT population	All randomized patients who use at least 1 dose of study drug and have any postdose headache severity or symptom assessments
mITT population	All ITT patients who treat a migraine attack within 4 hours of onset. The mITT population will be the primary analysis population
PPS	All mITT patients will be considered PPS if they do not have major protocol deviations which might impact the assessment of efficacy. Details will be specified in the SAP
SP	All randomized patients who use at least 1 dose of study drug, regardless of whether or not they underwent any study assessments. Patients will be evaluated by the drug they use, not by the drug to which they are randomized

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat; PPS = per protocol set; SAP = statistical analysis plan; SP = safety population.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or designee. SAS® software will be used to perform most or all statistical analyses.

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

Prior to locking and unblinding the database, a detailed statistical analysis plan (SAP) will be completed.

In general, we will use the following statistical methods unless otherwise specified (for definitions of [T1], [T2], and [T3], see Section 10.3.3.1):

- For efficacy analyses based on proportion, the logistic regression used in [T1] will be used (e.g., PROC GENMOD in SAS).
- When treatment effect (placebo, lasmiditan 50 mg, lasmiditan 100 mg, lasmiditan 200 mg) is in a statistical model, it will be regarded as a categorical variable.
- For safety analysis and demographics, only descriptive statistics will be presented and no statistical test will be conducted.
- Statistical tests will be conducted at a 2-sided significance level of 0.05. The 95% confidence interval will be presented if appropriate.
- No multiplicity adjustment for multiple tests (between the arms for the same efficacy objective, nor between the different objectives for the same arms) will be made except primary and two key secondary analyses ([T1], [T2], and [T3]).

We will use the following analysis population rules unless otherwise specified (see population definitions in Section 10.2):

- Protocol deviation will be based on all randomized and mITT.
- Demographics and Baseline characteristics will be based on mITT/ITT/safety population (SP).
- Efficacy analyses [T1], [T2], [T3], and MBS will be based on mITT/ITT/per-protocol set (PPS).
- Other efficacy will be based on ITT.
- Safety analyses (e.g., AE, laboratory assessments/vital signs) and treatment compliance will be based on SP.

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.

10.3.2.2. Patient Characteristics

Patient characteristics will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous measures (sample size, mean, standard deviation, minimum, median, max) and for categorical measures (sample size, frequency, and percentages).

Patient characteristics may include, but are not limited to: age, gender, height, weight, body mass index, and migraine history.

10.3.2.3. Concomitant Therapy

Frequency and percentages will be calculated by treatment for concomitant medication.

10.3.2.4. Treatment 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.

Electronic diary compliance will be summarized within each treatment group.

10.3.3. Efficacy Analyses

10.3.3.1. Primary and Secondary Analyses

The following statistical tests [T1] (primary), [T2] (key secondary), and [T3] (key secondary) will be conducted sequentially ([T1], [T2], then [T3]) by a gatekeeping method. This guarantees that the overall type 1 error across the set of primary and key secondary hypothesis tests is 0.05. Other assessments will not be part of the gatekeeping procedure.

- [T1] Primary: placebo vs. lasmiditan 200 mg (pain free at 2 hours) will be based on logistic regression.
- [T2] Key secondary: dose response of placebo, lasmiditan 50 mg, 100 mg, and 200 mg (pain free at 2 hours) will be based on Cochran-Armitage trend test.
- [T3] Key secondary: placebo vs. lasmiditan 100 mg (pain relief at 2 hours) will be based on logistic regression.

The analysis population for [T1], [T2], and [T3] under the gatekeeping procedure is the mITT.

For [T1], [T2], or [T3], if an analysis ([T1] or [T2] or [T3]) is not statistically significant, then all subsequent analyses will be conducted but will be designated as exploratory rather than confirmatory.

For the [T1] analysis, the statistical test will be based on placebo vs. lasmiditan 200 mg using the logistic regression model that includes treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and baseline usage of medications to reduce the migraine (Yes/No).

For the [T2] analysis, the Cochran-Armitage trend test will be based on placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg. The trend parameter is (0, 50, 100, and 200).

For the [T3] analysis, the statistical test will be based on placebo vs. lasmiditan 100 mg using the logistic regression model that includes treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and baseline usage of medications to reduce the migraine (Yes/No).

Other details, including additional covariates, if any, and the programming code for [T1], [T2], and [T3], and analysis methods for other secondary efficacy endpoints, will be specified in the SAP.

CCI [redacted]

10.3.5. Safety Analyses

10.3.5.1. 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 the site. 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 3 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 patients with TEAEs within each SOC and preferred term. Frequency counts will also be presented for patients with related TEAEs, and TEAEs by maximum severity. If multiple severities are reported for a given TEAE for a subject, the highest severity will be counted. Other details can be found in the SAP.

A summary of TEAEs for patients with CV risk factors will be created.

10.3.5.2. 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 summarized by treatment group.

10.3.5.3. Vital Signs

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse measurements will be taken when the patient is in a sitting position. 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.

10.3.5.4. 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 3, as appropriate.

10.3.5.5. Assessment of Driving Incidents

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

10.3.6. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.7. Subgroup Analyses

Subgroup analyses will be conducted using the following patient groups:

- Patients at risk of cardiovascular disease.
- Patients who use triptans within 3 months of screening.
- Patients who fail the most recent triptan at any time before screening.
- Patients who use migraine prevention therapy during the study.

The following tables, figures and listings will be created for the subgroup analyses:

- Demographics for the mITT.
- Efficacy analyses (pain free at 2 hours) for the mITT.
- Efficacy analyses (pain relief at 2 hours and MBS at 2 hours) for the mITT.
- Safety analyses (TEAE) for the SP.

Further detail (and other subgroup analyses, if any) will be specified 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

[EuroQol] The EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.

Hartmaier SL, Santanello NC, Epstein RS, Silberstein SD. Development of a brief 24-hour migraine-specific quality of life questionnaire. *Headache*. 1995;35(6):320-329.

Herdman M, Gudex C, Lloyd A, Janssen MF, Kind P, Parkin D, Bonsel G, Badia X. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-1736.

[IHS] International Headache Society, Headache Classification Subcommittee. The International Classification of Headache Disorders, 2nd edition. *Cephalagia*. 2004;24(Suppl 1):9-160.

[JHS] Japanese Headache Society Guideline: Clinical practice guideline for chronic headache 2013. Available at: http://www.jhsnet.org/GUIDELINE/gl2013/gl2013_main.pdf. Published 15 May 2013. Accessed January 11, 2019.

Labastida-Ramirez A, Rubio-Beltran E, Garrelds IM, Haanes KA, Chan KY, Kovalchin J, Johnson KW, Danser AHJ, Villalon CM, MaassenVanDenBrink A. Lasmiditan inhibits CGRP Release in the mouse trigeminovascular system. 18th International Headache Congress, Vancouver, Canada, Sept 7-10, 2017.

Lipton RB, Buse DC, Serrano D, Holland S, Reed ML. Examination of unmet treatment needs among persons with episodic migraine: results of the american migraine prevalence and prevention (AMPP) study. *Headache*. 2013;53(8):1300-1311.

Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology*. 2015;84(7):688-695.

Lipton RB, Kolodner K, Bigal ME, Valade D, Láinez MJ, Pascual J, Gendolla A, Bussone G, Islam N, Albert K, Parsons B. Validity and reliability of the Migraine-Treatment Optimization Questionnaire. *Cephalalgia.* 2009;29(7):751-759.

Posner K, Brown G, Stanley B, Brent DA, Yershova KV, Oquendo MA, Currier GW, Melvin GA, Greenhill L, Shen S, Mann JJ. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266-1277.

Ramadan NM, Skljarevski V, Phebus LA, Johnson KW. 5-HT1F receptor agonists in acute migraine treatment: a hypothesis. *Cephalalgia.* 2003;23(8):776-785.

Sakai F, Igarashi H. Prevalence of migraine in Japan: a nationwide survey. *Cephalagia.* 1997;17(1):15-22.

Santanello NC, Polis AB, Hartmaier SL, Kramer MS, Block GA, Silberstein SD. Improvement in migraine-specific quality of life in a clinical trial of rizatriptan. *Cephalalgia.* 1997;17(8):867-872.

Santanello NC, Hartmaier SL, Epstein RS, Silberstein SD. Validation of a new quality of life questionnaire for acute migraine headache. *Headache.* 1995;35(6):330-337.

Serrano D, Buse DC, Manack Adams A, Reed ML, Lipton RB. Acute treatment optimization inepisodic and chronic migraine: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache.* 2015;55(4):502-518.

Stewart WF, Lipton RB, Dowson AJ, Sawyer J. Development and testing of the Migraine Disability Assessment (MIDAS) Questionnaire to assess headache-related disability. *Neurology.* 2001;56(Suppl 1):S20–S28.

Stewart WF, Lipton RB, Kolodner K, Liberman J, Sawyer J. Reliability of the migraine disability assessment score in a population-based sample of headache sufferers. *Cephalalgia.* 1999;19(2):107-114.

Takeshima T, Ishizaki K, Fukuhara Y, Ijiri T, Kusumi M, Wakutani Y, Mori M, Kawashima M, Kowa H, Adachi Y, Urakami K, Nakashima K. Population-based door-to-door survey of migraine in Japan: the Daisen study. *Headache.* 2004;44(1):8-19.

Tfelt-Hansen PC, Diener, HC. Why should american headache and migraine patients still be treated with butalbital-containing medicine? *Headache*. 2012;52(4):672-674.

[WHO] World Health Organization, Headache disorder. Fact sheet, April 2016. WHO web site. Available at: http://www.who.int/en/news-room/fact-sheets/detail/headache-disorders. Accessed September 11, 2018.

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 adverse event 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.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
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/subject] nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
C-CASA	Columbia-Classification Algorithm of Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
CIOMS	Council for International Organizations of Medical Sciences
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.
CRS	clinical research scientist
CVD	cardiovascular disease
ECG	electrocardiogram
eCRF	electronic case report form

eDiary	electronic diary
EoS	end of study
EQ-5D-5L	EuroQol 5 dimension 5-level scale
FSH	follicle-stimulating hormone
GCP	good clinical practice
HRQoL	Health-Related Quality of Life
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICHD	International Classification of Headache Disorders
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 decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized 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.
IUD	intrauterine device
IUS	intrauterine system
IVRS/IWRS	interactive voice-response system/interactive web-response system
LLT	lowest level term
MBS	most bothersome symptom

MedDRA	Medical Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment Test
mITT	modified intention to treat
MQoLQ	Migraine Quality of Life Questionnaire
mToQ	Migraine Treatment Optimization Questionnaire
NIMH	National Institute of Mental Health
NSAIDs	non-steroidal anti-inflammatory drugs
PGI-C	Patient Global Impression of Change
PK/PD	pharmacokinetics/pharmacodynamics
PPS	per-protocol set: The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
QTc	corrected QT interval
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.
SOC	system organ class
SP	safety population
SUSARs	suspected unexpected serious adverse reactions
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: 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.
ULN	upper limit of normal
WHO	World Health Organization

Appendix 2. Clinical Laboratory Tests

Unscheduled or repeat blood chemistry, hematology, and urinalysis panels may be performed at the discretion of the investigator, as needed.

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
Platelets	Alanine aminotransferase (ALT)
Differential WBC absolute counts and/or % of:	Aspartate aminotransferase (AST)
Neutrophils	Blood urea nitrogen (BUN)
Lymphocytes	Creatinine
Monocytes	Uric acid
Eosinophils	Calcium
Basophils	Glucose, nonfasting
	Albumin
Urinalysis[a,b,c]	Cholesterol
Specific gravity	Creatine kinase (CK)
pH	Follicle stimulating hormone (FSH)[d]
Protein	
Glucose	**Pregnancy Test** (females only)
Ketones	
Blood	**Stored Samples**
Urine leukocyte esterase	Pharmacogenetic sample (genetic sample/DNA)

Urine drug screen

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] Microscopic examination of sediment performed only if abnormalities are noted on the routine urinalysis.

[d] Refer to Inclusion Criteria [8] in section 6.2.

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 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 (CIOMS) 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 specialistswith 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.

Electronic patient-reported outcome (ePRO) measures or other data reported directly by the patient are entered into an ePRO instrument at the time that the information is obtained (see Appendix 5). In these instances where there is no prior written or electronic source data at the site, the ePRO instrument record will serve as the source.

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.

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 subject 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 subject may include, for example, a paper diary to collect dosing date and time, menstrual cycle, concomitant therapy or an event.

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 or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study H8H-JE-LAIH 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[a]**
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. eDiary Assessments

	Visit 2	Predose	Postdose							
eDiary Assessment for attacks treated with study drug		**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**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	X
Presence or absence (yes or no) of accompanying symptoms: photophobia, phonophobia, nausea, and vomiting		X	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							X	
Disability		X	X	X		X			X	
PGI-C						X			X	
Treatment Satisfaction										X

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

Appendix 6. Protocol Amendment H8H-JE-LAIH(a) Summary: Randomized, Double-blind, Placebo-controlled Trial of Lasmiditan in a Single Migraine Attack in Japanese Patients Suffering from Migraine With or Without Aura – the MONONOFU study

Overview

Protocol H8H-JE-LAIH [Randomized, Double-blind, Placebo-controlled Trial of Lasmiditan in a Single Migraine Attack in Japanese Patients Suffering from Migraine With or Without Aura] has been amended to respond to inquiries and requests from the Pharmaceuticals and Medical Devices Agency (PMDA), received on 27 Feb 2019 upon clinical trial notification. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

Per request of PMDA, Lilly has made changes based upon the recommendation or suggestion as follow:

- Changed the description of the inclusion criterion [8] in order to clarify patient eligibility for the investigators.

Other changes and rationale for the changes made to this protocol are as follows:

- Added the abbreviated title of the study as the MONONOFU study.
- Deleted Google+ from the inclusion criterion [10] since the service is terminated.
- Replaced the Figure LAIH.2. in order to clarify the allowance period of these restricted rescue and recurrence medications.
- Changed the description of footnote d in Appendix 2 for clarify.

Revised Protocol Sections

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

Title

Protocol H8H-JE-LAIH(a)

RandoMized, DOuble-bliNd, PlacebO-coNtrolled Trial Of Lasmiditan in a Single Migraine Attack in Japanese Patients SuFfering from Migraine With or WithoUt Aura – the MONONOFU study

Title of Study:
Protocol H8H-JE-LAIH RandoMized, DOuble-bliNd, PlacebO-coNtrolled Trial Of Lasmiditan in a Single Migraine Attack in Japanese patients SuFfering from Migraine With or WithoUt Aura – the MONONOFU sutdy

6.2. Inclusion Criteria

[8] *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,~~ or intrauterine devices approved in Japan, or sterile partner during clinical trial period and until 30 days after the last dose of study medication and to report occurrences of pregnancy or suspected pregnancy to the investigator immediately.

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.

Male participants with pregnant female partners or female partners with child-bearing potential must agree to use a barrier method of contraception during clinical trial period and until 30 days after the last dose of study medication and to report occurrences of pregnancy or suspected pregnancy of their partner to the investigator immediately.

[10] 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 (e.g., Facebook, Twitter, LinkedIn~~, Google+~~, etc.) until the entire trial has completed.

7.2.1.1. Rescue/Recurrence Medication

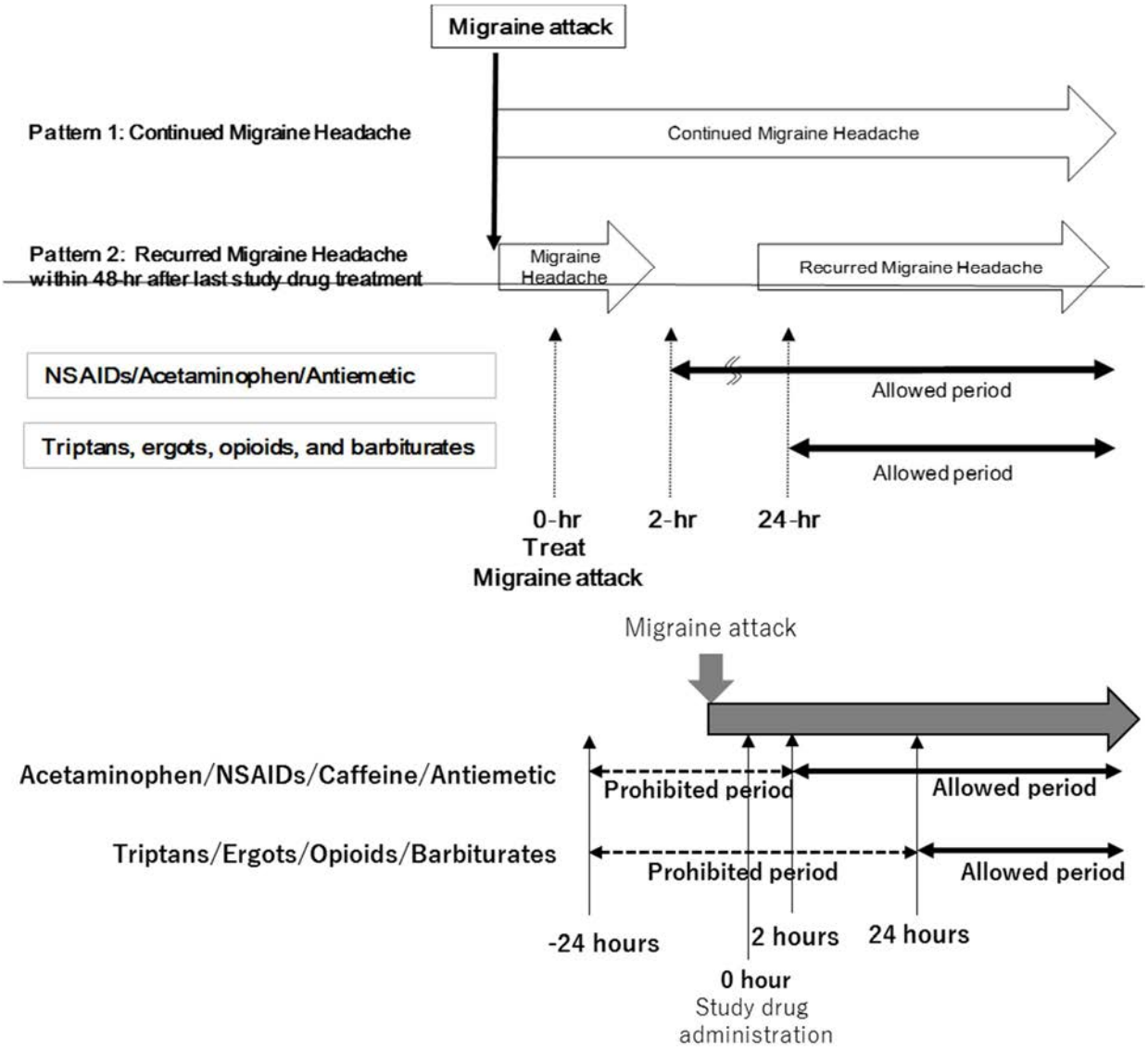


Figure LAIH.2. Allowance of restricted rescue/ recurrence medications.

Appendix 2. Clinical Laboratory Tests

[d] ~~Only for those who have shown cessation of menses at least in the past 12 months (excluding those confirmed from their medical record to be infertile due to a congenital or acquired condition such as hysterectomy or bilateral oophorectomy).~~Refer to Inclusion Criteria [8] in section 6.2.

Leo Document ID = 2d720f3e-eb67-4b77-99fe-8ccae1dfc4b1

Approver: PPD
Approval Date & Time: 06-Mar-2019 00:36:21 GMT
Signature meaning: Approved

Approver: PPD
Approval Date & Time: 06-Mar-2019 01:49:17 GMT
Signature meaning: Approved