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

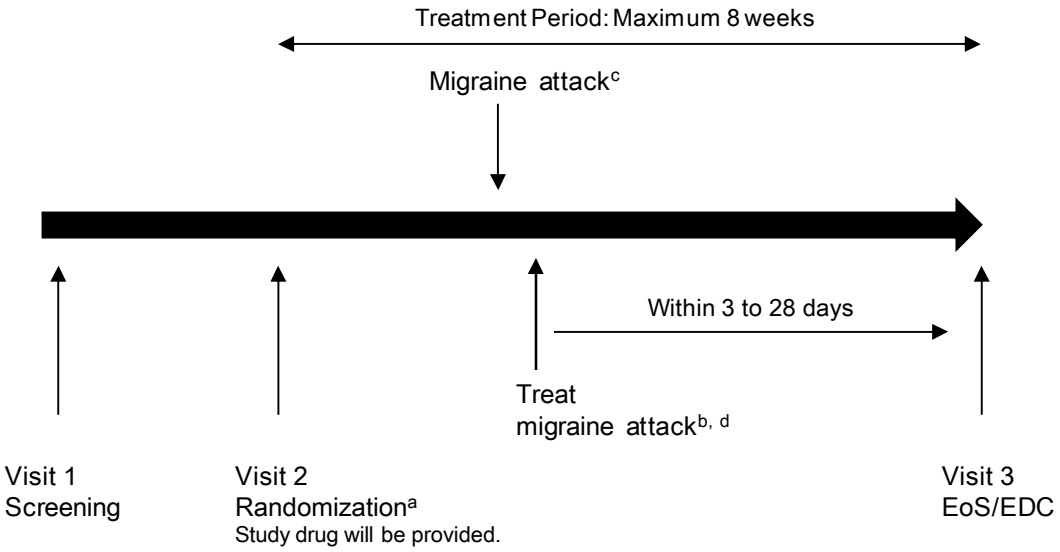
Table LAIH.2. Schedule of Activities

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.

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.



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).

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:

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

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.

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.

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

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.

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			

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.

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.

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,

- 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.

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

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.

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.

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

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

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	