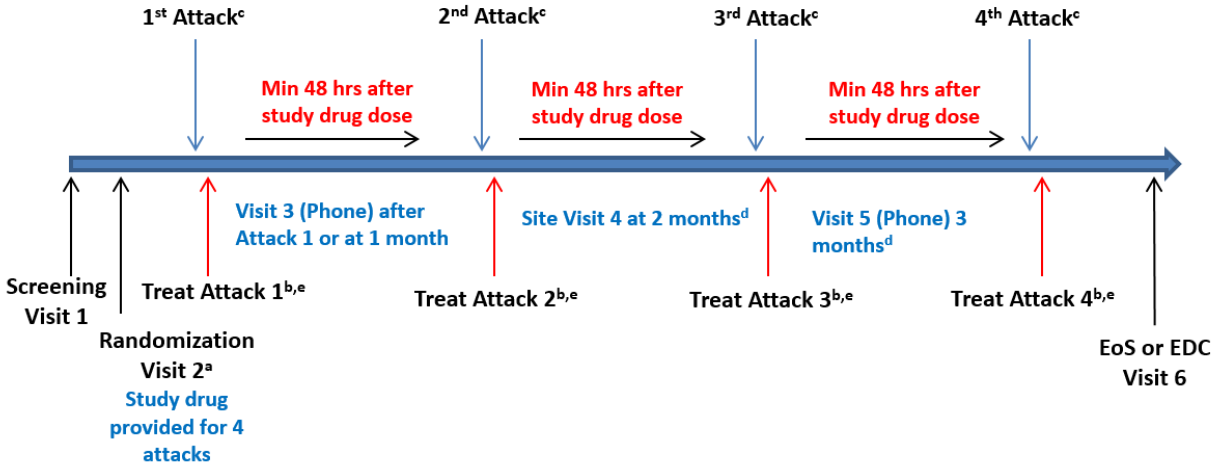
Objectives	Endpoints
Secondary, *Efficacy*, continued	
• To assess the probability of migraine relapse in patients treated with lasmiditan 200 mg and 100 mg compared to placebo	• The proportion of patients in each group with migraine recurrence at 24 and 48 hours during the first attack defined as return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

Table LAIJ.2.1. Schedule of Activities

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

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



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

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

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

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

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

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

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

Table LAIJ.5.1. Treatment Group Sequences

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

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

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

5.1.1. Screening (Visit 1)

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

5.5. Justification for Dose

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

Recording Use of Rescue/Recurrence Medication

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

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

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

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

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

9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient. Such events should be recorded on the AE page of the eCRF.

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

Investigators must document their review of each laboratory safety report.

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

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

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

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

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

The investigator answers yes/no when making this assessment.

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

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

9.2.1. Serious Adverse Events

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

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

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

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

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

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

10.3.4.2. Columbia-Suicide Severity Rating Scale

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

10.3.4.3. Vital Signs

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

10.3.4.4. Labs

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

10.3.4.5. Assessment of Driving Accidents

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

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Other Analyses

10.3.7.1. Health Economics

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

10.3.7.2. Subgroup Analyses

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

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

Additional details are available in the SAP.

10.3.8. Interim Analyses

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

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

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

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

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

5.1.2. Randomization (Visit 2)

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

5.1.3. Treatment Period

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

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

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

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

Study governance considerations are described in detail in Appendix 3.

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

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

Overview

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

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

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

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

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

Summary of Study Design:

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

Treatment Arms and Duration:

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

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

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

Number of Patients:

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

Statistical Analysis:

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

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

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

6. Study Population

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

6.1. Inclusion Criteria

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

Type of Patient and Disease Characteristics

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

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

[3] migraine onset before the age of 50 years

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

[5] MIDAS score ≥11

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

Patient Characteristics

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

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

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

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

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

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

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

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

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

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

9.1.3. Appropriateness of Assessments

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

been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

Refer to the IB.

9.4. Safety

The safety assessments are described below.

9.4.1. Electrocardiograms

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

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

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

9.4.2. Vital Signs

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

11. References

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

5.2. Number of Patients

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

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

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

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

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

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

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

Inclusion of the control group

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

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

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

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