

Protocol H8H-MC-LAHW(c)

A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients With Migraine -
PIONEER-PEDS2

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Title Page

Protocol H8H-MC-LAHW(c) A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine - PIONEER-PEDS2

EudraCT: 2019-004379-38
EU trial number: 2023-506724-85-00

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Lasmiditan (LY573144)

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Protocol Amendment (c) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-116974

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment b	07-Aug-2020
Amendment a	09-Mar-2020
Original Protocol	02-Dec-2019

Amendment [c]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to consolidate EU country-specific requirements into the main protocol.

Section # and Name	Description of Change	Brief Rationale
Title Page	Added heading.	For navigation purposes and per template.
Protocol Amendment Summary of Changes Table	Added section.	Per protocol template and EU CTR.
1.1. Synopsis	Corrected the study acronym in the Protocol Title to match the title page - PIONEER-PEDS2.	Correction.
1.1. Synopsis	Added - Regulatory Agency Identifier Numbers - Study Population, and - Ethical Considerations of Benefit/Risk.	Per EU CTR.
2.3. Benefit/Risk Assessment	Added subsections - Management of risks for this study, and - Overall benefit-risk conclusion.	
6.1. Study Intervention(s) Administered	Added - definition of study intervention and information about authorization of study intervention as defined by EU Clinical Trial Regulation - subsection Packaging and labeling.	
7.2.1. Discontinuation of Inadvertently Enrolled Participants	Removed section.	Per Lilly policy.
8.3.1.1. Suspected Unexpected	Updated text for section.	Per EU CTR.

Section # and Name	Description of Change	Brief Rationale
Serious Adverse Reactions		
9.4.1. General Considerations	Added information for the handling of missing, unused, and spurious data.	Per EU CTR.
10.1.1. Regulatory and Ethical Considerations	Added bullet for reporting of significant issues related to participant safety, participant rights, or data integrity.	Per EU CTR.
10.1.4. Data Protection	Updated text.	Per EU CTR.
10.1.6. Dissemination of Clinical Study Data	Updated text.	
Section 10.5. Appendix 5: Country-specific Requirements	Added appendix per EU CTR submission requirements and added requirements for Germany and France.	
10.6. Abbreviations and Definitions	Updated header for a more accurate description of content Added definitions for • abuse • authorized IMP • authorized AxMP • AxMP • GDPR • IMP • medication error • misuse, and • NIMP. Updated the definition for SUSARs.	
10.8. Protocol Amendment Summary	Removed document history table and added text explaining the location in the beginning of the document.	Per Lilly template.
Appendices	Updated numbering.	Appendix addition.
Several sections	Minor editorial changes.	Minor, therefore not described.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine – PIONEER-PEDS2

Protocol Number: H8H-MC-LAHW

Short Title: A 12-Month Study of Lasmiditan, a Treatment for Migraine, in Pediatric Patients

Regulatory Agency Identifier Number(s):

EudraCT: 2019-004379-38

EU trial number: 2023-506724-85-00

Rationale:

To evaluate the safety and tolerability of long-term intermittent use of lasmiditan for the acute treatment of migraine in pediatric patients for up to 12 months.

Overall Design:

This is a prospective, randomized, open-label, 12-month study in children and adolescents with a diagnosis of migraine who previously enrolled in and completed Study H8H-MC-LAHX (LAHX) or Study H8H-MC-LAHV (LAHV). Study participants will be stratified by age group (6 to CCI years and CCI to <18 years based on age at time of screening for Study LAHX or LAHV) and randomized in a CCI ratio to treatment with CCI doses comparable to 100 mg and 200 mg adult exposure.

During a 12-month, open-label treatment period, study participants may use lasmiditan to treat CCI migraine attacks CCI on an outpatient basis. Dosing with lasmiditan, outcomes, use of concomitant medications, and adverse events will be recorded in a CCI. Rescue medication may be used beginning 2 hours after lasmiditan dosing. Patients may use 1 dose of lasmiditan in a CCI. Participants may use their usual treatment in the event they choose not to take lasmiditan for an individual attack.

Study participant visits to the clinic are scheduled at CCI and 12 months after study enrollment.

Site personnel will conduct assessments at each visit as detailed in the Schedule of Activities.

Study Population:

In general, an individual may take part in this study if they

- are between 6 and <18 years of age at the time of screening for Study LAHX or Study LAHV
- have a minimum body weight of 15 kg, and

- are able to swallow a tablet.

In general, an individual may not take part in this study if they

- have a history or clinical evidence of heart disease present from birth
- have used opioids or barbiturate-containing analgesics more than 3 times per month for the treatment of pain in more than 2 of the past 6 months, and
- have a history of other primary or secondary headache disorders or migraine subtypes, including sporadic or familial hemiplegic migraine and migraine with brainstem aura.

Ethical Considerations of Benefit/Risk:

Given the need for additional safe and effective medications for the acute treatment of migraine in children and adolescents, and considering the measures taken to minimize risk to participants, the potential benefit-risk balance for this study is acceptable for testing in this population.

Disclosure Statement:

This is an open-label study and participants will be randomized to CCI doses comparable to exposures of 100 mg and 200 mg in adults.

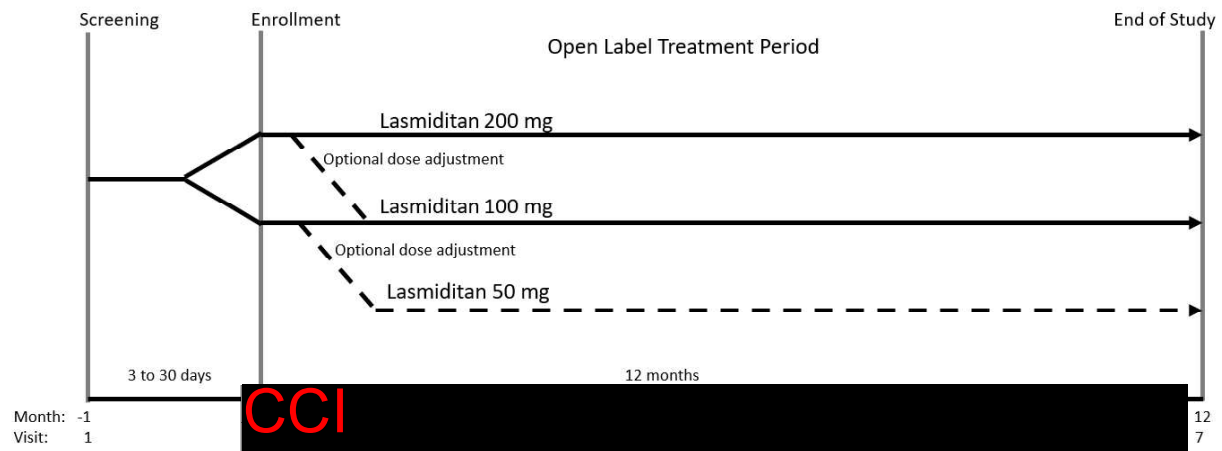
Number of Participants:

The sample size for this study is not based on statistical or power considerations. This is an open-label study for patients who previously enrolled in and completed Study H8H-MC-LAHX or Study H8H-MC-LAHV. Therefore, the maximum number of eligible participants is determined by the number of participants completing the aforementioned studies. At a minimum, the study is expected to include at least CCI treating, on average, at least 1 migraine per month for 6 months, and at least CCI treating, on average, at least 1 migraine per month for 12 months.

Data Monitoring Committee: Yes

All safety data will be reviewed by a data monitoring committee external to Lilly.

1.2. Schema



Abbreviation: mg = milligrams.

1.3. Schedule of Activities

	Screening ^{ab}	CCl						Month 12 EoS	ED	Notes
Visit	1							7		
Target Interval Since Previous Visit (Days)								90±7		
Procedure/Assessments										
Informed consent/assent	X									Consent and assent form signed by patient and parent or guardian. Minor participants must be re-consented if they reach the age of legal consent during the course of the study.
Inclusion/exclusion	X									Eligibility confirmed at CCl including results of laboratory evaluations.
Physical examination	X						X	X	X	Complete physical examination, excluding pelvic and rectal examination.
Medical History	X									To include only events that are ongoing or new since participation in LAHX or LAHV.
Vital signs	X	X	X	X	X	X	X	X	X	
Height/weight	X	X	X	X	X	X	X	X	X	
Review of immunization history	X									Investigators should review the participant's vaccine record to assess the risk of under-immunization. No adjustment to routine vaccination is required.
Menstrual status	X		X	X	X	X	X	X	X	
Confirmation of study eligibility		X								Review lab results and confirm study eligibility prior to randomization.
Randomization		X								
Study medication dispensed		X	X	X	X	X	X			Study medication can be dispensed in between scheduled visits as needed; not to exceed dosage needed to treat CCl migraine attacks CCl.
Study procedures training		X								Site to instruct patient and parent/guardian on study procedures, including administration of study IP and completion of CCl.
Study procedures review			X	X	X	X	X			Site to review study procedures with patient and parent or guardian as needed.
Study medication collected			X	X	X	X	X	X	X	Returned IP reconciled with dosing details captured in CCl.
CCl										
	X	X	X	X	X	X	X			

	Screening ^{ab}	CCl				Month 12 EoS	ED	Notes
Visit	1					7		
Target Interval Since Previous Visit (Days)						90±7		
Concomitant medications (Medicine Log)	X	X	X	X	X	X	X	Collected and captured verbatim at Visit 1; captured in CCl and reviewed at all other visits, including unscheduled study visits, if they occur.
Adverse events (Health Log)	X	X	X	X	X	X	X	Collected and captured verbatim at Visit 1; captured in CCl and reviewed at all other Visits, including unscheduled study visits, if they occur.
Treatment with lasmiditan and efficacy outcomes (Migraine Treatment Log)		X	X	X	X	X	X	Captured in CCl
CCl								
Clinical Laboratory Tests								
Hematology	X	X	X	X	X	X	X	
Clinical chemistry	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	Urine sample to be divided into 2 aliquots. In the event of a positive leukocyte esterase, the second sample will have a microscopic analysis and possible urine culture.
Pregnancy test for females of childbearing potential	X	X	X	X	X	X	X	Urine pregnancy test. A positive urine test must be followed by a serum pregnancy test for confirmation.
Gonadal hormones	X		X		X	X	X	Estradiol (females) or testosterone (for males) will be collected for the assessment of pubertal status.
Urine drug screen	X	X	X	X	X	X	X	For patients aged ≥10 years.
CCl								
Scales & Questionnaires								
PedMIDAS	X		X	X	X	X	X	Self-administered by patient and parent or guardian.

	Screening ^{ab}	CCI					Month 12 EoS	ED	Notes
Visit	1						7		
Target Interval Since Previous Visit (Days)							90±7		
C-SSRS Since Last Visit – Children's Version	X		X	X	X	X	X	X	Adapted for the assessment of the ideation and behavior categories only (Intensity of Ideation and Lethality of Behavior sections removed). The C-SSRS will be administered by trained site staff to patients ≥7 years old.
Self-Harm Supplement Form	X		X	X	X	X	X	X	
Self-Harm Follow-Up Form	X		X	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Cogstate Brief Battery					X		X	X	Supervised by trained test administrator;
PedsQL 4.0 Generic Core Scales	X				X		X	X	patient to complete battery on tablet/computer
HCRU (recall period “in the last 6 months”)	X				X		X	X	Patient-reported scale; Young Child, Child, or Teen Version according to age at screening.
HCRU (recall period “since your last visit”)									Administered by site staff.
Assessment of Driving Accidents/Violations – Since Last Visit	X		X	X	X	X	X	X	Administered by site staff.
									Administered by site staff to patients who are of legal age to drive, per local regulations.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; **CCI** ; ED = early discontinuation; EoS = End-of-Study; HCRU = health care resource utilization; IP = investigational product; PedMIDAS = Pediatric Migraine Disability Assessment Scale; PedsQL = Pediatric Quality of Life Inventory.

Note: Sites should make every attempt to schedule patient visits within the defined window. Exceptions to these windows may be granted under certain circumstances with prior approval of the Lilly clinical research physician (CRP) or designee.

- ^a Screening evaluations may be repeated once if necessary in the event of screen failure (See Section 5.4).
- ^b Identical assessments completed within **90** days of Visit 1 at EoS visit for LAHX or LAHV may serve as screening assessments for LAHW.

2. Introduction

2.1. Study Rationale

Study H8H-MC-LAHW (Study LAHW) will evaluate the safety and tolerability of long-term, intermittent use of lasmiditan for up to 12 months for the acute treatment of migraine in pediatric patients.

2.2. Background

Migraine is one of the most common neurological conditions in pediatrics, occurring in 7.7% of children and adolescents under 20 years of age (Abu-Arafeh et al. 2010). Migraine has a negative impact on function and quality of life (Stang and Osterhaus 1993; Powers et al. 2003; Hershey et al. 2004; Kabbouche and Gilman 2008; Rocha-Filho and Santos 2014).

The goal of migraine treatment in the pediatric population is quick resolution of the headache with minimal side effects. The first line of treatment is over-the-counter medication (Hämäläinen et al. 1997; Lewis et al. 2002). There are few approved prescription medications (triptans) for the pediatric population, and only 1 approved for children aged 6 to 11. There is a need for additional safe and effective medications for the acute treatment of migraine in children and adolescents (Patterson-Gentile et al. 2018).

Lasmiditan is a centrally penetrant, high-affinity selective 5-HT_{1F} receptor agonist developed specifically for the acute treatment of migraine. Lasmiditan selectively targets 5-HT_{1F} receptors on neurons in the central and peripheral trigeminal system, decreasing neuropeptide release and inhibiting pain pathways, including the trigeminal nerve (Nelson et al. 2010; Vila-Pueyo 2018).

2.3. Benefit/Risk Assessment

Lasmiditan may provide therapeutic benefit to children and adolescents with migraine. Lasmiditan is approved in the United States for the acute treatment of migraine, with or without aura, in adults. In adults with migraine with or without aura, lasmiditan (50 mg, 100 mg, and 200 mg) has been shown to be an effective treatment based on the primary endpoints of pain freedom and freedom from the most bothersome symptom (selected from nausea, photophobia, or phonophobia at the beginning of the migraine attack) at 2 hours postdose (Kuca et al. 2018; Goadsby et al. 2019). Additional evidence of efficacy was observed on multiple secondary measures of pain relief (2 hours), sustained pain freedom (24 hours), functioning (2 hours), and Patient Global Impression of Change (2 hours), as well as time to onset of pain relief, pain freedom, and freedom from associated symptoms.

In Study LAHW, pediatric patients will have the option to treat CCI migraine attacks CCI with lasmiditan for 12 months. Patients will be initially randomized to receive CCI doses comparable to 100 mg and 200 mg exposures in adult patients. However, patients may request 1 dose adjustment for tolerability after treating at least 3 migraine attacks at the randomized dose.

As a centrally penetrant and neurally active drug, lasmiditan use is associated with neurologic treatment-emergent adverse events (TEAEs), with the most common being dizziness,

paresthesia, somnolence, fatigue, nausea, hypoesthesia, and muscle weakness. Lasmiditan is generally well-tolerated, and the vast majority of adverse events (AEs) are mild to moderate in severity and of limited duration.

Management of risks for this study

Section 8.2 addresses the management of known potential risks of lasmiditan.

Overall benefit-risk conclusion

Given the need for additional safe and effective medications for the acute treatment of migraine in children and adolescents, and considering the measures taken to minimize risk to participants, the potential benefit-risk balance for this study is acceptable for testing in this population.

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

3. Objectives and Endpoints

Objectives	Endpoints*
<u>Primary</u>	
To evaluate the safety and tolerability of long-term intermittent use of lasmiditan for the acute treatment of migraine in pediatric patients.	• Nature, proportion, and severity of TEAEs by treated attack. • Proportion of discontinuation due to AEs.
<u>Key Secondary</u>	
To evaluate the efficacy of intermittently dosed lasmiditan in the treatment of multiple migraine attacks over time in pediatric patients.	• Proportion of treated attacks with pain freedom at 2 hours after dosing for each 3-month period. • Proportion of treated attacks with pain relief at 2 hours after dosing for each 3-month period. • Proportion of treated attacks with MBS-freedom at 2 hours after dosing for each 3-month period.

Abbreviations: AE = adverse event; MBS = most bothersome symptom; TEAE = treatment-emergent adverse event.

*Additional safety and secondary efficacy endpoints described in Sections [8.1](#) and [8.2](#).

4. Study Design

4.1. Overall Design

Study LAHW is a prospective, randomized, open-label, 12-month study in children and adolescents with a diagnosis of migraine who previously enrolled in and completed Study LAHX or Study LAHV.

4.1.1. Screening Visit

At the Screening Visit (Visit 1), the patient and parent or guardian will sign the informed consent form (ICF) and assent form prior to any study assessments, examinations, or procedures being performed. With the exception of laboratory results, study eligibility for each patient will be evaluated (Section 5.1 and Section 5.2). All screening procedures will be performed according to the Schedule of Activities (SoA). Once laboratory data are available and reviewed, the site will contact the patient to schedule an Enrollment Visit (Visit 2) or to request further screening procedures.

4.1.2. Enrollment Visit

In the Enrollment Visit (Visit 2), study eligibility for each patient will be confirmed based on all inclusion and exclusion criteria assessed in Visit 1 and laboratory test results. Patients whose eligibility is confirmed will receive education regarding study procedures. Patients will be randomized, and study medicine will be dispensed.

4.1.3. Open-Label Treatment Period

Study participants may treat CCI, moderate, or severe migraine attacks CCI with lasmiditan. Administration is limited to a single dose of lasmiditan in a CCI, and rescue medication is permitted 2 hours after lasmiditan dosing. Exceptions are noted in Section 6.5.1. Study participants will also record dosing of lasmiditan, outcomes, use of other medication, and AEs in CCI.

If participants choose not to treat an individual attack with lasmiditan, they may use their usual treatment for migraine attacks.

Study participant visits to the clinic are scheduled at CCI and 12 months after study enrollment.

Site personnel will conduct assessments at each visit according to the SoA.

4.1.4. End of Study

The End-of-Study (EoS) visit will be at 12 months.

4.2. Scientific Rationale for Study Design

This study will provide important information on the long-term safety and tolerability of intermittent use of lasmiditan to treat migraine attacks in children and adolescents.

The 12-month duration of the study is considered appropriate to assess long-term safety, and the randomized doses include the highest efficacious dose in the adult population. During the treatment period, participants will visit the clinic at regularly scheduled intervals (CCI and 12 months) for study assessments, procedures, and study medication accountability and compliance.

The study will also provide additional information about the effectiveness of lasmiditan.

4.3. Justification for Dose

Study LAHW will include CCI doses to achieve exposures comparable to the 100 mg and 200 mg adult exposure. This will provide safety and tolerability data for the 2 higher doses of lasmiditan being evaluated for the intermittent treatment of multiple migraine attacks in the pediatric population. If needed for tolerability, patients may decrease dose once to a CCI dose corresponding to 100 mg or 50 mg adult exposure after treating at least 3 attacks with randomized dose (see Section 6.6). See Table LAHW.1 for detail on CCI dosing to achieve exposures comparable to adult doses of 50 mg, 100 mg, and 200 mg.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the duration of the 12-month study, including the last scheduled procedure shown in the SoA.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

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

5.1. Inclusion Criteria

Patients are eligible to be included in the study if they have previously completed Study LAHX or Study LAHV, and all of the following criteria apply at Screening and/or Enrollment:

Type of Patient and Disease Characteristics

- [1] Patient was between 6 and <18 years of age inclusive at the time of screening into Study LAHX or Study LAHV.
- [2] The patient has a minimum body weight of 15 kg.
- [3] The patient is able to swallow a tablet.
- [4] For patients taking migraine preventive medication, treatment regimen is stable and has been taken for at least 3 months prior to Visit 1.

Informed Consent and Patient Agreements

- [5] The patient and patient's parent or guardian must understand the nature of the study. The patient's parent or guardian must sign an ICF and the patient must sign an informed assent document as required by local regulations.
- [6] The patient and patient's parent or guardian are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.
- [7] The patient is male or female; if female, must agree to abide by the following guidance:
 - Females of childbearing potential (started menses, to include any duration or amount of spotting) 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 partneruntil CC days after the last dose of study medication.
 - Females of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, and postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

- [8] The patient and patient's parent or guardian must 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 until notification that the study has completed. Examples of these sites include:

- Facebook,
- Twitter,
- Snapchat,
- Instagram, and
- Google+.

5.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at Screening and/or Enrollment:

Medical Conditions

- [9] Patient has a history or clinical evidence of congenital heart disease, suspected or confirmed.
- [10] Patient has an electrocardiogram (ECG) showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular disease risk.
- [11] Within 6 months of Screening, patient had myocardial infarction, unstable angina, percutaneous coronary intervention, and/or coronary artery bypass graft.
- [12] Patient has planned cardiovascular surgery or percutaneous coronary angioplasty, or has a history of stroke.
- [13] Patient has any liver tests outside the normal range at Screening that are clinically significant. Alanine aminotransferase (ALT) >2X upper limit of normal (ULN), total bilirubin level (TBL) >1.5X ULN, or alkaline phosphatase (ALP) >2X ULN must be discussed and judged not clinically significant by Lilly Medical prior to enrollment.

NOTE: Patients with TBL >1.5X ULN are not excluded if they meet all of the following criteria for Gilbert syndrome:

- Bilirubin is predominantly indirect (unconjugated) at Screening (direct bilirubin within normal limits)
 - Absence of liver disease
 - ALT, aspartate aminotransferase (AST), and ALP $\leq$ 1X ULN at Screening
 - Hemoglobin not significantly decreased at Screening.
- [14] Patient has, in the judgment of the investigator, a psychiatric disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition that would interfere with adherence to study requirements or safe participation in the trial. This includes a current or historical diagnosis of a substance use disorder.
- [15] Patient is, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

[16] At Screening:

- patient has answered “yes” to either Question 4 or Question 5 on the “Suicidal Ideation” portion of the Columbia-Suicide Severity Rating Scale (C-SSRS), or has answered “yes” to any of the suicide-related behaviors on the “Suicidal Behavior” portion of the C-SSRS, and
- the ideation or behavior occurred within the past month.

[17] Patient is pregnant or breastfeeding.

[18] Patient has, in the judgment of the investigator, an acute, serious, or unstable medical condition or a history or presence of any other medical illness that would preclude study participation.

Prior and Concomitant Therapy/Substances of Abuse

[19] Patient has used opioids or barbiturate-containing analgesics >3X per month for the treatment of pain in more than 2 of the past 6 months.

[20] Patient has known allergies to lasmiditan, related compounds, or any components of the formulation.

[21] Patient has a positive urine drug screen for any substances of abuse.

Note: Positive results are acceptable if due to regular and medically acceptable use of a prescribed medication, such as a benzodiazepine for sleep or anxiety or stimulants for Attention Deficit Hyperactivity Disorder. One retest is allowed if the urine drug screen is positive, at the investigator’s discretion.

Diagnostic Assessments

[22] Patient has a history of other primary or secondary headache disorders or migraine subtypes, including sporadic or familial hemiplegic migraine and migraine with brainstem aura, previously known as basilar-type migraine. A history of tension-type headache or medication overuse headache as defined by ICHD-3 is permitted.

[23] Patient has a history of traumatic head injury associated with significant changes in the quality or frequency of their headaches, including new onset of migraine following traumatic head injury or a history of posttraumatic headache.

[24] Patient has a known history of intracranial tumors or developmental malformations including Chiari malformations.

Prior/Concurrent Clinical Trial Experience

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

[26] Patient has participated, within the last 30 days, in a clinical study involving an investigational product other than lasmiditan. If the previous investigational product has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.

Other Exclusions

- [27] Patient is legally or mentally incapacitated.
- [28] Patient is a child of investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
- [29] Patient is a child of Lilly employees.
- [30] In the opinion of the investigator or sponsor, patient is unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Patients can consume their usual diet throughout the study. When treating a migraine attack, patients will be asked to complete CCI assessments at the time of dosing, 2 hours, 24 hours, and 48 hours after taking lasmiditan. (CCI [REDACTED]). If possible, patients should complete study assessments as close to prespecified timepoints as possible.

During the treatment of a migraine attack, patients may have some transient restrictions on their usual activities due to the experience of pain and symptoms of a migraine attack, requirements to complete study procedures, and effects of study treatment. Patients should not engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after each dose of lasmiditan, as described in the ICF and assent.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Based on the clinical judgment of the investigator, individuals who fail to qualify at Enrollment CCI may be rescreened for this study at a later date. If changes in circumstances have allowed a patient to be rescreened, a complete Screening Visit 1 must be repeated. However, if the Rescreen Visit is within CCI days from the original Screening Visit and the initial screening failure was a result of specific out-of-range laboratory findings, then only those assessments should be repeated and not the entire lab panel. Only 1 rescreening visit is permitted. If rescreening is performed, the parent or guardian and participant must sign a new ICF and assent form, and the participant will be assigned a new participant number.

6. Study Intervention

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Lasmiditan is authorized as defined by EU Clinical Trial Regulation and not used according to the EU authorization in the pediatric population and in this study.

Participants will be randomized in a CCI ratio at study entry to treatment with CCI doses corresponding to the 100 mg and 200 mg adult exposure (referred to throughout as lasmiditan 100 mg and lasmiditan 200 mg). The lasmiditan dose may be reduced 1 time during study participation in the event of tolerability concerns, after treatment of at least 3 migraine attacks at the randomized dose (see Section 6.6). Study participants may use lasmiditan to treat CCI migraine attacks CCI on an outpatient basis.

Table LAHW.1 shows the planned treatment regimens CCI. Doses to achieve 50 mg exposure will only be used for dose modification if required; 50 mg dose exposure is not a randomized dose.

CCI

If the patient is <12 years of age, or if deemed necessary for older children, the parent or guardian, or another responsible adult, will maintain control and inventory of the drug supplies and ensure that study medication is properly administered.

The investigator or his or her designee is responsible for:

- Explaining the correct use of lasmiditan to the patient, parent or guardian, and site personnel.
- Ensuring that patients are able to swallow whole tablets.
- Verifying that instructions are followed properly.
- Maintaining accurate records of lasmiditan dispensing and collection.

- Returning all unused medication to Lilly or its designee.

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation/Handling/Storage/Accountability

At each visit, patients will be dispensed lasmiditan to treat [REDACTED] migraine attacks. Based on use, patients may request additional lasmiditan supply in between scheduled study visits, not to exceed quantity needed to treat CCI [REDACTED] migraine attacks CCI [REDACTED]. Lasmiditan will be supplied to the clinical sites in blister packs.

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

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manually or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.

Study intervention will be affixed with a clinical label in accordance with regulatory requirements.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Study participants will be stratified by age group (6 to CCI [REDACTED] years and CCI [REDACTED] to <18 years) and randomized to receive either lasmiditan 100 mg or lasmiditan 200 mg. In order to reduce potential bias, all participants will be centrally assigned to randomized study intervention using an interactive web-response system (IWRS).

Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site. The site will contact the IWRS prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form (CRF), if required. Study intervention will be dispensed at the study visits according to the SoA. Returned study intervention should not be redispensed to the participants.

6.4. Study Intervention Compliance

Compliance with dosing instructions will be assessed at all visits by documentation of returned, unused investigational product. Deviations from the prescribed dosage regimen should be recorded in the electronic CRF (eCRF).

6.5. Concomitant Therapy

Any medication, device, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of Screening or receives during the study must be recorded along with the:

- reason for use,
- dates of administration including start and end date/time, and
- dosage information including dose and frequency (see Section 8.2.1).

Any changes in dosage or new medications added as a result of intercurrent illness during the patient's time on study must be recorded in the CRF. If a patient requires the initiation of migraine prophylaxis (concomitant medication to reduce the frequency of migraine episodes) or a change in ongoing migraine prophylaxis after Screening/Visit 1, they should be withdrawn from the study.

Use of any investigational treatment other than lasmiditan is prohibited for the duration of a patient's participation in the study from Screening/Visit 1 through EoS.

6.5.1. Additional Migraine Therapy

Use of additional medication for treatment of migraine pain or associated symptoms will be permitted after completion of the 2-hour assessments. The patient may use their usual headache therapy, or the investigator may advise each subject to use an alternative suitable medication.

However, the following medications should not be used until 24 hours after study medication administration:

- triptans,
- ergots,
- opioids, and
- barbiturates.

The date and time of medication administration, as well as the name and dosage regimen of the medication, must be recorded in the CCI [REDACTED].

6.6. Dose Modification

Tablets dispensed to achieve the prescribed dose may be adjusted, CCI [REDACTED], in the event of changes that move the patient from the CCI [REDACTED].

For each patient, the lasmiditan dose may be reduced 1 time during study participation in the event of tolerability concerns, after treatment of at least 3 migraine attacks at the randomized

dose. Patients randomized to 200 mg may decrease dose to 100 mg, and patients randomized to 100 mg may decrease dose to 50 mg. Once made, this adjustment will persist for the remainder of study participation, with no further decreases or increases. Unscheduled office visits may occur at any time to monitor patient safety and/or tolerability at the discretion of the investigator.

6.7. Intervention after the End of the Study

At the completion of Study LAHW, patients will be referred to their local physician or treatment centers for migraine treatment as clinically indicated.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up, and for any further evaluations that need to be completed.

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

- ALT or AST >8X ULN,
- ALT or AST >5X ULN for more than 2 weeks,
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio >1.5,
- ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%),
- ALP >3X ULN,
- ALP >2.5X ULN and TBL >2X ULN, or
- ALP >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

Participants who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the CRF.

Discontinuation of the investigational product for signs of suicidal ideation or behavior should be considered by the investigator when a participant meets 1 of the following conditions and after risk assessment:

- answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, or
- answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue study intervention.

Other possible reasons for discontinuation of study intervention include:

- positive result on urine drug screen (see detail in Exclusion Criteria 21),
- pregnancy, and
- the participant or the participant's parent or guardian requests to discontinue lasmiditan.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request,
- at the request of his/her designee (for example, parents or legal guardian),
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- if the participant becomes pregnant during the study,
- if the participant enrolls in any other clinical study involving an investigational product or enrolls in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant requires a change in, or addition of, preventive medication for migraine, then discontinuation from the study occurs prior to introduction of the new agent.

If a study participant discontinues between scheduled visits, if possible, there will be an early discontinuation visit within cc days of treatment discontinuation. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time. Unused study medication should be returned to the site at that time for proper documentation and disposal.

7.3. Lost to Follow-Up

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

Information about discontinuation of specific sites or of the study are in [Appendix 1](#).

8. Study Assessments and Procedures

The SoA describes study procedures and their timing, including tolerance limits for timing.

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

Appendix 3 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

8.1. Efficacy Assessments

8.1.1. Patient **CCl**

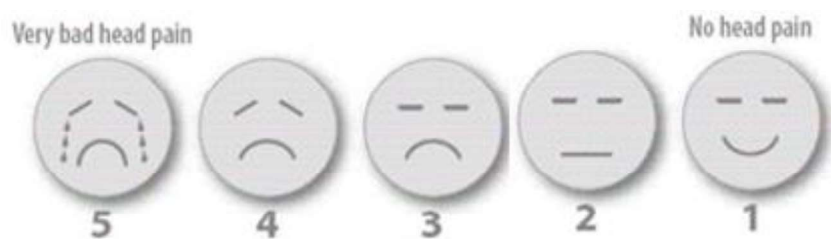
Patients will use the Migraine Treatment Log section in the **CCl** to record a number of efficacy outcomes including pain intensity, freedom from associated symptoms of migraine (nausea, photophobia, and phonophobia), whether patients were asleep at 2 hours after taking lasmiditan, interference of migraine symptoms in normal activities, sustained pain freedom, time to pain relief, and use of rescue medication within 48 hours of dosing.

If the patient is <12 years of age, or if deemed necessary for older children, then a parent or guardian, or other responsible adult who has knowledge of the conduct of this study, may supervise or assist with completion of **CCl** entries.

At each study visit, site staff should review **CCl** entries. **CCl** entries serve as source documentation of efficacy assessments. Based on completeness and consistency of patient entered data, sites should provide further instruction to patients and their parent/guardian regarding complete and accurate recording in the **CCl** during intervals between study visits.

8.1.1.1. Pain Severity

Migraine pain severity will be assessed using a 5-Face Pain Scale at the time of treatment and 2, 24, and 48 hours after taking lasmiditan. Migraine pain intensity is defined as follows: face 1 = no pain; face 2 = mild pain; faces 3 to 4 = moderate pain; face 5 = severe pain (Maunuksela et al. 1987). The participant must select the number corresponding to the face that represents their current pain severity.

Figure 1. 5-Face Pain Scale

As patients can treat migraine attacks when pain is mild, moderate, or severe, responses to the 5-Face Pain Scale are used to calculate the following outcomes:

Assessment	Definition
Pain freedom	A reduction in baseline pain from mild (Face 2), moderate (Faces 3 and 4), or severe (Face 5) to no pain (Face 1).
Pain relief	A reduction in baseline pain from moderate (Faces 3 and 4) or severe (Face 5) to mild (Face 2) or no pain (Face 1), mild (Face 2) to no pain (Face 1), or patient is asleep.
Sustained pain freedom	No headache pain (Face 1) at 2 hours after treatment, with no use of rescue medication and no recurrence of mild, moderate, or severe headache pain within the specified time point (24 or 48 hours).

8.1.1.2. Associated Symptoms of Migraine

The presence of associated symptoms of migraine will be captured in the **CCI** at the time of treatment and at 2 hours after treatment.

Participants will be asked to identify whether they are experiencing nausea (yes/no), phonophobia (yes/no), and/or photophobia (yes/no), and if so, which is the most bothersome symptom to them.

8.1.1.3. Interference in Daily Activities

A single **CCI** item is used to capture the magnitude of migraine interference with normal activities at the time of treatment and at 2 hours after treatment with the question:

“How much is your migraine stopping you from doing what you usually do (such as play or do schoolwork)?”

Responses will be recorded on a 4-point numeric rating scale at 2 hours (0 = not at all; 1 = a little; 2 = a lot; 3 = completely).

8.1.1.4. Time to Meaningful Pain Relief

A single **CCI** item is used to capture the time to onset of relief.

8.1.1.5. Use of Rescue Medication

Details on use of other medication will be provided in the **CCI** (see Section 8.2.1 for more information on documentation of concomitant medication).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

The investigator is responsible for the appropriate medical care of patients during the study. Unscheduled or repeat safety assessments may be performed at the discretion of the investigator, as needed.

Safety and tolerability assessments in pediatric patients will include the following standard assessments:

- vital signs including blood pressure (BP), pulse rate (PR), and body temperature,
- AE monitoring, including TEAEs, SAEs, and discontinuation due to AEs,
- clinical chemistry, hematology, and urinalysis,
- onset of puberty,
- assessment of growth including height and weight,
- assessment of cognition, and
- suicidality, measured by the C-SSRS-Children's Version.

8.2.1. Patient CCI

Patients will record AEs and concomitant medication use throughout study duration in CCI (Health Log and Medicine Log sections, respectively). If the patient is <12 years of age, or if deemed necessary for older children, then a parent or guardian, or other responsible adult who has knowledge of the conduct of this study, may supervise or assist with completion of CCI entries.

At each study visit, site staff should review CCI entries. CCI entries serve as source documentation for AEs and concomitant medication. Based on completeness and consistency of patient entered data, sites should provide further instruction to patients and their parent/guardian regarding complete and accurate recording in the CCI during intervals between study visits.

Adverse Event Collection

Patients will record AEs that occur during the treatment period in the Health Log section of the CCI. Information will include start and end dates of AEs and severity. At every post-screening visit, site personnel will review the patient CCI with the patient/guardian and record any change in the pre-existing condition(s) and any new conditions as AEs.

For each AE, investigators should record the following via the eCRF:

- date and time of onset,
- date and time of resolution,
- severity, and
- their assessment of the potential relatedness of each AE to investigational product.

Concomitant Medication Collection

Participants will be asked to record all medication use, including changes in dosing of previous medications and use of other medication to treat migraine, in the Medicine Log section of the

CCI. At every postscreening visit, site personnel will review the patient CCI with the patient/guardian and record concomitant medications.

For each concomitant medication, investigators should record the following via the eCRF:

- name of medication (including vaccines, over-the-counter medicine, vitamins, or herbal supplements),
- reason for use,
- start day and time and end day and time of medication use, and
- dose and frequency.

8.2.2. Physical Examinations

For each participant, a complete physical examination will be performed at Visit 1 (Screening) and at Visit 7 (EoS). The examination will exclude pelvic and rectal examinations, but will include assessments of the:

- cardiovascular,
- respiratory,
- gastrointestinal, and
- neurological systems.

A targeted physical examination may be repeated at the investigator's discretion at any time a patient presents with physical complaints.

8.2.3. Vital Signs

Vital signs collected during the study include systolic and diastolic BP, PR, and temperature (see schedule in SoA). Blood pressure and PR measurements will be taken when the patient is in a sitting position. Blood pressure readings will be collected using the appropriately sized pediatric BP cuffs.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (for example, television or cell phones).
- Vital signs will consist of 1 PR, 1 temperature, and 3 BP measurements (3 consecutive BP readings will be recorded at intervals of at least 1 minute).

Any clinically significant findings from vital sign measurements that result in a diagnosis should be reported to Lilly or its designee as an AE via the eCRF.





8.2.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and see the SoA for the timing and frequency. All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the SoA.

Use of local anesthetics (for example, EMLA cream) consistent with local prescribing information are permitted during the study visits to ease discomfort associated with venipunctures.

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

Investigators must document their review of each laboratory safety report.

8.2.5.1. Hepatic Safety Monitoring

If a study participant experiences elevated ALT $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or TBL $\geq 2X$ ULN, liver testing (Section 10.4) should be repeated within 3 to 5 days, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

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

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

Alkaline phosphatase laboratory results may be out of the normal range in pediatric patients because of normal bone growth processes. Collection of a blood sample for bone ALP may be requested by the sponsor as a reflex to test if the ALP result is high.

8.2.6. Cognition

A baseline measure of cognition assessed by the Cogstate Pediatric Brief Battery (©2018 Cogstate Ltd [WWW]) was previously obtained from patients in either Study LAHX or Study LAHV. Additional measures of cognition will be obtained at CCI (CCI) and at EoS (12 months). This assessment is a brief 15- to 18-minute computerized cognitive assessment, administered by qualified site personnel, that measures processing speed, attention, visual learning, and working memory.

This battery of cognitive assessments was selected because the assessments are brief, resistant to practice effects, culture- and language-neutral, and has well-established reliability and validity for the repeated assessment of cognitive function in children (Mollica et al. 2005). Evidence supports its use in children with chronic pain (Bredlau et al. 2015) and in other indications such as mild traumatic brain injury, schizophrenia, and acquired immunodeficiency syndrome-dementia complex (Maruff et al. 2009).

8.2.7. Assessment of Driving Accidents and Violations – Since Last Visit

Sites will administer a brief assessment of involvement in car accidents, or citations for driving violations, to those patients at the legal age of driving, per local regulations (see Schedule of Activities for administration schedule).

8.2.8. Suicidal Ideation and Behavior Risk Monitoring

Assessment of suicidal ideation and behavior will be conducted using the C-SSRS – Children’s Version (Posner et al. 2011) as required by the FDA’s Division of Neurology for use in clinical trials involving all drugs for neurological indications.

Nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS, but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

8.2.8.1. Columbia-Suicide Severity Rating Scale - C-SSRS

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health (NIMH) trial group (TASA) for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorization of suicidal events.

The Children’s Version of the C-SSRS will be administered to all patients ≥ 7 years of age by qualified site personnel according to the SoA (Posner et al. 2011). For this study, the scale has been adapted (with permission from the scale authors) to include only the portion of the scale that captures the occurrence of the 11 preferred ideation and behavior categories. The Intensity of Ideation and Lethality of Behavior sections are removed.

Any suicidal behavior or suicidal ideation per Items 4 or 5 (active suicidal ideation with some intent to act either without specific plan or with specific plan and intent) shall require prompt referral of the patient for urgent evaluation by an appropriately qualified health care professional.

8.2.8.2. Self-Harm and Follow-Up Supplement Forms

As part of the C-SSRS, the Self-Harm Supplement and Follow-Up forms are to be completed for each event if the patient reports 1 or more self-harm events. The Self-Harm Supplement Form is an administrative form to denote the presence of any self-harm events reported at that administration and is used to trigger the Self-Harm Follow-Up form in the data capture system. The Self-Harm Follow-Up form is a series of questions that provides a more detailed description of the behavior cases.

8.2.9. Growth Monitoring

Height and weight will be collected as described below and according to the SoA to allow for the identification of potential effects on growth and development:

- Height measurements will be made using a stadiometer. Height measurements must be measured in triplicate and recorded to 1 decimal place without rounding.
- Weight measurements must be taken once and recorded to 1 decimal place without rounding.
- Instruments used for measuring height and weight should be appropriately and regularly calibrated.
- All measurements of height and weight should be made without shoes and after the removal of any heavy personal items (that is, large jewelry, wallets, coats, etc.).

8.2.10. Puberty and Menstrual Status

Pubertal status will be assessed based on results of blood estradiol and testosterone levels done at Screening, CCI and 12-month visits, and menstrual history (for females). Pubertal status will be assessed by the sponsor based on results of blood hormone levels and, for females, menstrual status.

8.3. Adverse Events and Serious 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 in cases of AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue before completing the study. The patient should be followed up 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 and patient assent form are signed, study site personnel will record, via the CRF, the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s), occurrence, and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment or a study procedure, taking into account the disease, concomitant treatment, or pathologies. A "reasonable possibility" means that there is a potential cause-and-effect relationship between the investigational product and the AE.

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

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via the CRF, clarifying, if possible, the circumstances leading to discontinuation of treatment.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 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, or
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Examples of such medical events include:

- allergic bronchospasm requiring intensive treatment in an emergency department 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 CRF and assessed for serious criteria. The SAE-reporting to the sponsor begins after the participant 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 according to SAE-reporting requirements and timelines (see Section 9.4.5) 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. 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. Participants with a serious hepatic AE should have additional data collected using the CRF.

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. All pregnancies will result in discontinuation from the study.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the participant 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 or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

8.3.1.1. Suspected Unexpected Serious Adverse Reactions

The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards/Independent Ethics Committees, and investigators.

8.3.2. Pregnancy

Any pregnancies occurring within 1 month following administration of study medication will be reported. To fulfill regulatory requirements, any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Abnormal pregnancy outcomes are considered SAEs.

8.4. Treatment of Overdose

There is limited clinical trial experience with lasmiditan overdose. There were no instances of overdose in the clinical pharmacology program. In the Phase 2 and Phase 3 clinical studies, the maximum dose received by any adult patient in a 24-hour period was 600 mg. No TEAEs were reported following any instance of dosing >400 mg (in a 24-hour period).

Doses exceeding the maximum therapeutic dose may be associated with increased incidence and/or severity of AEs, therefore, the patient should be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

The self-reported questionnaires will be administered according to the SoA in countries where the questionnaires have been translated into the native language of the region and linguistically validated.

8.10.1. Pediatric Migraine Disability Assessment Scale

The Pediatric Migraine Disability Assessment Scale (PedMIDAS) will capture disability due to migraine. The PedMIDAS is based on the adult version of the MIDAS; however, the instrument is specifically designed to quantify headache-related disability in school-aged children and adolescents (Stewart et al. 1999; Hershey et al. 2001). The PedMIDAS is a patient-reported outcome instrument and is intended to be self-administered by the patient and their parent/caregiver. It can be completed in collaboration, but the answers need to be confirmed with the patient. Neither the principal investigator nor the site staff should administer or complete this instrument.

The instrument consists of 6 items in which the number of disabled days due to headache over the past 3 months are captured, including full days missed from school, partial days missed from school, functionally impaired days in school, functionally impaired days at home, inability to participate in extracurricular and leisure activities, and functionally impaired days of extracurricular and leisure activities, which sum to the PedMIDAS Total Score. Higher values are indicative of a greater level of disability due to headache. This instrument is considered reliable and valid.

In addition to the 6 items included in the PedMIDAS scale, 2 additional questions are asked to capture frequency and severity of migraine:

- On how many days in the last 3 months did you have a headache?
- On a scale of 0 to 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be)

8.10.2. Pediatric Quality of Life Inventory™

The PedsQL 4.0 Generic Core Scales are a general health measure designed to specifically evaluate quality of life and functioning in children and adolescents (Varni et al. 2001; Powers et al. 2003).

The instrument consists of 23 items measuring the level of impairment over the past month, and addresses 4 functional domains: physical, emotional, social, and school. In addition, 2 summary

scores can be produced, with 8 of the items measuring physical health and 15 of the items measuring psychosocial health.

The instrument has age-specific questionnaires to ensure the validity and reliability within developmentally-appropriate groups; hence there are specific forms for those in the following age ranges: 2 to 4 years, 5 to 7 years (Young Child), 8 to 12 years (Child), and 13 to 18 years (Teen) (Varni et al. 2001, 2002; Schwimmer et al. 2003). The form administered at all assessments throughout study duration is based on patient's age at Visit 1. For ages 5 to 7 years (Young Child), site personnel should read the instrument to the patient, and the patient will indicate their response by pointing to the appropriate face in the response guide. For ages 8 to 12 years (Child) and 13 to 18 years (Teen), patients should complete this on their own, without assistance, as much as possible. Further details on administration are found in the user manual, and in the study manual of operations.

Lower scores are indicative of greater functional impairment. The instrument is considered sensitive and appropriate for use in acute or chronic illnesses (Varni et al. 2001, 2002).

8.10.3. Health Care Resource Utilization

Health care resource utilization associated with medical encounters will be collected in the CRF by the investigator and study site personnel for all participants throughout the study. Site personnel are to ask the questions of the participant, parent, or guardian at each visit. If any hospitalizations are reported, sites should conduct the appropriate follow-up and submit as an SAE report as required by the study. Healthcare encounters specific to the conduct of this study (such as protocol-mandated procedures, tests, and encounters) are not to be included in the count of health care resource utilization.

Protocol-mandated procedures, tests, and encounters are excluded. The data collected may be used to conduct exploratory economic analyses and will include:

- number of hospital emergency room visits and visits related to a migraine,
- number and duration (total days) of hospital overnight visits and visits related to a migraine, and
- number of other healthcare professional visits (physician of any specialty, nurse, rehabilitation specialist, physical therapist, psychologist or counselor, urgent care center, etc.) and visits related to a migraine.

8.11. Immunizations

At Visit 1, investigators should review the participant's vaccine record to assess the risk of under immunization. No adjustment to routine vaccination is required.

9. Statistical Considerations

9.1. Statistical Hypotheses

No inferential statistical analyses are planned.

9.2. Sample Size Determination

The sample size for this study is not based on statistical or power considerations. This is an open-label study for patients who previously enrolled in and completed Study LAHX or Study LAHV. Patients are randomized to receive CCI doses comparable to the 100 mg and 200 mg exposures in adults. While some patients may experience dose reduction to a 50 mg dose during the duration of the trial, our ability to assess safety and efficacy of that dose are likely to be limited due to small sample size.

9.3. Populations for Analyses

Table LAHW.2. Populations for Analysis

Population	Description
Enrolled	All patients who sign informed consent.
Randomized	All patients randomized to study medication. Patients will be evaluated by the treatment group to which they are randomized.
Evaluable	All randomized patients who administer at least 1 dose of study medication. Patients will be included in the treatment group (LTN 50 mg, LTN 100 mg, or LTN 200 mg) respective to the treatment they receive.

Abbreviations: LTN = lasmiditan; mg = milligrams.

9.4. Statistical Analyses

9.4.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Details of statistical analysis methods will be described in the statistical analysis plan (SAP) document.

Unless otherwise specified, safety and efficacy analyses will be conducted on the evaluable population. Patients will be included in the treatment group respective to the treatment they receive. For analyses by migraine attacks, the treatment group will be defined respective to the treatment the patient received for that attack. For analyses by visit, the treatment group will be defined respective to the treatment they last received.

Change from baseline analyses will include patients who have a baseline and a postbaseline measurement. Unless otherwise specified, baseline will be defined as the last measurement prior to the first dose of lasmiditan. Specifically, baseline will be obtained from the parent study (LAHX or LAHV) for patients who received at least 1 dose of lasmiditan in the parent study. Otherwise, baseline will be obtained from Study LAHW.

For continuous data, descriptive statistics will be presented, including the mean, standard deviation, 95% confidence intervals for the mean, median, minimum, maximum, and sample size. For categorical data, sample size, frequency counts, proportions, and 95% confidence intervals for the proportion will be presented.

Unless otherwise specified, all analyses will be conducted on the overall population (patients 6 to <18 years of age) and in the subgroups of patients 6 to CCI years of age and patients CCI to <18 years of age. The subgroup for age will be defined by the age of the patient at the Screening Visit for the parent study, LAHX or LAHV.

Efficacy data will be censored after use of additional medication for rescue. For patients who are asleep at any given timepoint after dosing, all pain-related outcomes will be assumed to have achieved pain relief, but not assumed to have achieved pain freedom.

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses are described in the final CSR.

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

9.4.2. Participant Disposition

The number and proportion of patients in each analysis population will be summarized by treatment group. Additionally, the number and proportion of patients who complete the EoS Visit will be summarized by treatment group.

9.4.3. Patient Characteristics

Patient characteristics will be summarized by treatment group.

The following patient characteristics at Screening/Visit 1 may include, but are not limited to:

- demographics (age, sex, race, ethnicity, height, weight, body mass index, and geographic region),
- parent study (LAHX or LAHV),
- migraine history,
- pubertal status,
- menstrual status, and
- disability (PedMIDAS Total Score).

9.4.4. Concomitant Therapy

The number and proportion of concomitant medication use and rescue medication use will be summarized by treatment group.

Concomitant medications are those taken during the study from Screening/Visit 1 to EoS/Visit 7. Rescue medications are concomitant medications for treatment of migraine or associated symptoms of migraine that are taken within 48 hours after dosing with lasmiditan.

9.4.5. Safety Evaluation

9.4.5.1. Adverse Events

Treatment-emergent adverse events are defined as reported AEs that first occurred or ongoing events that worsen in severity within 48 hours after dosing with study medication. For each TEAE, the reported severity level of the event will be determined by patient or physician opinion.

The number of TEAEs as well as the number and proportion of patients who experienced at least 1 TEAE will be summarized using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms nested within each system organ class by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit. Treatment-emergent adverse events by maximum severity will be summarized by treatment group and visit. All AEs, SAEs, and AEs that lead to discontinuation of study medication will be summarized by treatment group and visit.

Additionally, the proportion of treated migraine attacks associated with TEAEs, SAEs, and AEs that lead to discontinuation of study medication will be summarized by treatment group and visit.

9.4.5.2. Extent of Exposure

Extent of exposure will be summarized quarterly and for CCI 12 months. Summarizations will be performed by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and will include the following:

- number of treated migraine attacks (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg)
- proportion of patients who treated at least 1 migraine attack
- average number of treated migraine attacks per month
- proportion of patients who treat, on average, at least 1 migraine attack per month

9.4.5.3. Vital Signs

Change from baseline for BP, pulse, and temperature will be summarized by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit.

Categorical shifts from baseline in BP and pulse will be summarized by treatment group and visit. The categorical shifts will be defined by age groups (6 to <10 years of age, 10 to <12 years of age, 12 to <15 years of age, and 15 to <18 years of age), and additional details will be provided in the SAP.

CCI

9.4.5.5. Laboratory Tests

Age appropriate parameters to assess laboratory values and clinical measurements will be used. Change from baseline in laboratory parameters will be summarized by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit.

In addition, the number and proportion of patients with high or low results based on age appropriate reference ranges will be summarized by treatment group and visit for each parameter.

A low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any postbaseline visit. A high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any postbaseline visit.

9.4.5.6. Cognition

Baseline cognition domain scores (processing speed, attention, visual learning, and working memory) obtained from the parent study (Study LAHX or Study LAHV) will be used as the baseline scores for Study LAHW.

Postbaseline scores will be summarized as observed and change from baseline by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit (CCI and Month 12) for each cognitive domain.

The reliable change index will be calculated and summarized by treatment group and visit for each cognitive domain. The reliable change index is a measurement of the magnitude of change relative to the expected variation. The expected variation is calculated from a normative dataset sampled from an age-matched healthy population of children and adolescents aged 4 to 17. Separate expected variations were calculated for each individual year given maturational changes in cognition over the course of child and adolescent development.

The number and proportion of patients who report AEs and TEAEs that represent possible effects on cognition will be summarized by treatment group and visit using MedDRA preferred terms nested within each system organ class.

Additional details will be provided in the SAP.

9.4.5.7. Suicide-Related Thoughts and Behaviors

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring during treatment, based on the C-SSRS, will be summarized by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit. In addition, the number and proportion of patients who experienced at least 1 of various composite measures will be presented. These include:

- suicidal behavior such as:
 - completed suicide,
 - nonfatal suicidal attempts,
 - interrupted attempts,
 - aborted attempts, and

- preparatory acts or behavior
- suicidal ideation such as:
 - active suicidal ideation with specific plan and intent,
 - active suicidal ideation with some intent to act without specific plan,
 - active suicidal ideation with any methods (no plan) without intent to act,
 - nonspecific active suicidal thoughts, and
 - the wish to be dead, and
- suicidal ideation or behavior.

9.4.5.8. Growth Monitoring

Change from baseline for height, weight, and body mass index adjusted by number of treated migraine attacks will be summarized by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit.

9.4.5.9. Puberty and Menstrual Status

Puberty and menstrual status data will be listed for all of the randomized population.

9.4.6. Efficacy Evaluation

9.4.6.1. Secondary Endpoints

All efficacy analyses will be summarized for the evaluable population by the number of migraine attacks treated with lasmiditan. The summaries will include sample size (total number of treated migraine attacks), frequency counts, proportions of treated attacks, and 95% confidence intervals for the proportion. These endpoints will be summarized by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg). Summaries for the lasmiditan 50 mg treatment group will be exploratory due to expected limitations in sample size. Summaries will also be presented by quarter.

Secondary efficacy endpoints include proportions of treated migraine attacks with:

- pain freedom at 2 hours postdose,
- pain relief at 2 hours postdose,
- freedom from the most bothersome symptom at 2 hours postdose,
- freedom from nausea, photophobia, and phonophobia at 2 hours postdose,
- migraine interference with normal activities of ‘not at all,’ ‘a little,’ ‘a lot,’ and ‘completely’ at 2 hours postdose,
- sustained pain freedom at 24 hours postdose,
- sustained pain freedom at 48 hours postdose, and
- rescue medication use within 48 hours postdose.

The proportions of patients with each of the previously mentioned endpoints in $\leq 25\%$ and $>25\%$, $\leq 50\%$ and $>50\%$, and $\leq 75\%$ and $>75\%$ of their migraine attacks treated with lasmiditan during the study will be summarized by treatment group. Summaries will also be presented by quarter. Additional analyses will assess pain freedom at 2 hours in only those attacks treated when pain was moderate to severe.

Time to pain relief on the first treated migraine attack will be summarized using a Kaplan-Meier analysis by treatment group.

9.4.6.2. Health Outcome Endpoints

Summaries will be provided for the evaluable population for the following health outcome endpoints:

- PedMIDAS Total Scores, frequency, and severity of migraine,
- PedsQL item scores, functional domain scores, and summary scores, and
- healthcare resource utilization (number of hospital emergency room visits, hospital overnight stays, and other healthcare professional visits).

These endpoints will be summarized by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and visit. Summaries for the lasmiditan 50 mg treatment group will be exploratory.

9.5. Interim Analyses

Interim analyses for safety are planned for this trial and will be reviewed by an independent data monitoring committee (DMC). Details of these interim analyses will be specified in the DMC Charter and the interim analysis plan.

9.5.1. Data Monitoring Committee

A DMC will monitor the overall safety of this trial. The DMC will consist of members external to Lilly. This DMC will follow the rules defined in the DMC Charter, focusing on potential and identified risks for lasmiditan and for this class of compounds. Data monitoring committee membership will include, at a minimum, specialists with expertise in pediatrics, statistics, and other appropriate specialties.

The DMC will be authorized to review safety results by treatment group from interim analyses prior to database lock. The DMC may recommend stopping the study for safety, modifying the study for safety, or continuing the study with no modifications.

While the DMC may request to review efficacy data to investigate the benefit/risk relationship in the context of safety observations for ongoing patients in the study, no information regarding efficacy will be communicated. Details of the DMC, including its operating characteristics, will be documented in the DMC Charter.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
 - consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines,
 - applicable International Council for Harmonisation (ICH) good clinical practice (GCP) guidelines, and
 - applicable laws and regulations.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an investigational review board (IRB)/independent ethics committee (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
 - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
 - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
 - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
 - reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

10.1.2. Financial Disclosure

Investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study. Minor participants must be reconsented if they reach the age of legal consent during the course of the study in order to continue participating.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and must be kept on file.

Participants who are rescreened must sign a new ICF and the parent or guardian must sign a new assent form.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

A DMC external to Lilly will be formed.

10.1.6. Dissemination of Clinical Study Data**Reports**

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on a printed CRF or an eCRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents. The sponsor is responsible for granting electronic access to an eCRF and an electronic Clinical Outcome Assessment (eCOA).
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based

Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques, are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of participants are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for one year after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data will be collected by the participant/parent or guardian via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Additionally, eCOA data are directly recorded into a laptop or tablet device (CogState Brief Battery). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

Data collected via the sponsor-provided data capture system(s) will be stored at third-parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.

Additionally, eCOA data, such as cognition assessment, will be directly recorded by the patient into a computer. The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

10.1.9. Study and Site Closure

10.1.9.1. Discontinuation of the Study

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

10.1.9.2. Discontinuation of Study Sites

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

10.1.10. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in this section will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or as required by local regulations.

Hematology^{a,b}	Clinical Chemistry^{a,b}
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin	ALP
Mean cell hemoglobin concentration	AST
Leukocytes (WBC)	ALT
Neutrophils, segmented	BUN
Lymphocytes	Creatinine
Monocytes	Uric acid
Eosinophils	Calcium
Basophils	Glucose (nonfasting)
Platelets	Albumin
	Total protein
Urinalysis^{a,b}	
Specific gravity	
pH	
Protein	Other Tests
Glucose	Serum pregnancy test ^a
Ketones	Urine pregnancy test (local)
Bilirubin	Urine drug screen ^a
Urobilinogen	Gonadal hormone ^a (estradiol for females and testosterone for males)
Nitrite	
Blood	
Leukocyte esterase ^c	
Urine culture ^c	
Microscopic analysis ^c	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; RBC = red blood cell; WBC = white blood cell.

^a Assayed by sponsor-designated laboratory.

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

^c Urine sample to be divided into 2 aliquots. In the event of a positive leukocyte esterase, the second sample will have a microscopic analysis and possible urine culture.

10.3. Appendix 3: Sampling Summary

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

Protocol H8H-MC-LAHW Sampling Summary

Purpose	Planned ^a Blood Volume per Sample (mL)	Maximum ^b Number of Samples	Planned ^b Total Amount (mL)
Screening tests ^b	4.0	3	12.0
Standard laboratory tests ^b	2.5	10	25.0
Gonadal Hormones	4.0	2	8.0
Total			45.0
Hepatic monitoring ^c	3-30	-	3-30

^a Actual amount, number, or quantities may vary slightly due to unanticipated circumstances.

^b Additional samples may be drawn if needed for safety purposes.

^c Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly Medical.

10.4. Appendix 4: Liver Safety: Suggested Actions and Follow-Up Assessment and Study Intervention Rechallenge Guidelines

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the sponsor.

Hepatic Monitoring Tests

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

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

^a Assayed by Lilly-designated or local laboratory.

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

10.5. Appendix 5: Country-specific Requirements

Revisions per country-specific requirements are identified by ~~strikethroughs~~ and the use of underscore.

All deletions are identified by ~~strikethroughs~~ and all additions are identified by underscore.

10.5.1. Germany

The information in this section will apply to all investigational sites in Germany.

The purpose of this section is to provide clarifications regarding

- concomitant therapy
- participant discontinuation/withdrawal from the study, and
- adjustments to study procedures in response to the Covid-19 pandemic, based on regulatory agency feedback.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
6.5. Concomitant Therapy	Added clarification for co-administration with serotonergic drugs, medicines that lower heart rate, and combination with alcohol or other CNS depressants.	
7.2. Participant Discontinuation/Withdrawal from the Study	Added serotonin syndrome as a criterion for discontinuation.	
10.7. Appendix 7: Allowable Changes to Study Procedures due to Significant Environmental Regional Disruption	Changed header and text to reflect this is only applicable due to Covid-19 pandemic.	

Protocol Section 6.5. Concomitant Therapy

Any medication, device, or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of Screening or receives during the study must be recorded along with the:

- reason for use,
- dates of administration including start and end date/time, and
- dosage information including dose and frequency (see Section 8.2.1).

Caution is required in case of co-administration of lasmiditan with serotonergic drugs or medicines that may lower the heart rate. In addition, lasmiditan should be used with caution if used in combination with alcohol or other CNS depressants.

Any changes in dosage or new medications added as a result of intercurrent illness during the patient's time on study must be recorded in the CRF. If a patient requires the initiation of migraine prophylaxis (concomitant medication to reduce the frequency of migraine episodes) or

a change in ongoing migraine prophylaxis after Screening/Visit 1, they should be withdrawn from the study.

Use of any investigational treatment other than lasmiditan is prohibited for the duration of a patient's participation in the study from Screening/Visit 1 through EoS.

Protocol Section 7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request,
- at the request of his/her designee (for example, parents or legal guardian),
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons,
- if the participant becomes pregnant during the study,
- if the participant enrolls in any other clinical study involving an investigational product or enrolls in any other type of medical research judged not to be scientifically or medically compatible with this study, or
- if the participant requires a change in, or addition of, preventive medication for migraine, then discontinuation from the study occurs prior to introduction of the new agent.

Lasmiditan should be discontinued if serotonin syndrome is suspected or confirmed.

If a study participant discontinues between scheduled visits, if possible, there will be an early discontinuation visit within CC days of treatment discontinuation. See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time. Unused study medication should be returned to the site at that time for proper documentation and disposal.

Protocol Section 10.7. Appendix 7: Allowable Changes to Study Procedures due to Covid-19 Pandemic Significant Environmental Regional Disruption

~~There may be times of exceptional circumstances, such as~~ Individual, site, or regional restrictions due to the Covid-19 pandemic, s or natural disasters, which may cause disruptions to the conduct of the study, specifically to the ability of participants to attend onsite visits as scheduled. Written permission from the sponsor is required prior to implementing procedures outlined in this appendix. The changes to procedures documented in this appendix are temporary measures intended to be used as permitted by local regulation, only during periods of local restrictions. Once restrictions are no longer present, the sites should discontinue the use of these mitigations and return to the standard implementation of the study as outlined in the main protocol.

In such a situation, please follow the guidance below:

- 1) For each visit, sites will document how visit was conducted (telephone, virtual, or onsite), to allow description of changes to study conduct due to Covid-19 pandemic significant environmental disruption.

- 2) Patients should complete Visits 1, CCI 7, or early discontinuation in person, as specified in the SoA (Section 1.3). Patients have up to 7 days to complete Visit 1, and up to CCI days to complete Visits CCI 7, or early discontinuation, per the SoA. However, as specified in the note to the SoA, if the Covid-19 pandemic ~~extenuating circumstances~~ prevents conduct of in-person visits, the Lilly clinical research physician (CRP) or designee can extend the allowable window to conduct these visits in full.

Note: Sites should make every attempt to schedule patient visits within the defined window. Exceptions to these windows may be granted under certain circumstances with prior approval of the Lilly CRP or designee.

10.5.2. France

The information in this section will apply to all investigational sites in France.

The purpose of this section is to provide clarifications regarding

- exclusion criteria
- concomitant therapy
- serious adverse event (SAE) reporting, and
- urine pregnancy test inclusion in the enrollment visit.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
1.3. Schedule of Activities	Added a urine pregnancy test at enrollment Visit	
5.2. Exclusion Criteria	Made changes to criteria 9 and 27.	
6.5. Concomitant Therapy	Added cautionary statements for concomitant therapy.	
8.3.1. Serious Adverse Events	Provided clarification for the timing of SAE alerts to Lilly or its designee.	

Protocol Section 1.3. Schedule of Activities

	Screening ab						Month 12 EoS	ED	Notes
Visit	1						7		
Target Interval Since Previous Visit (Days)							90±7		
Procedure/Assessments									
Pregnancy test for females of childbearing potential	X	<u>X</u>	X	X	X	X	X	X	Urine pregnancy test. A positive urine test must be followed by a serum pregnancy test for confirmation.

Protocol Section 5.2. Exclusion Criteria

- [9] Patient has a history or clinical evidence of congenital heart disease, suspected or confirmed, or clinical evidence of uncontrolled hypertension.
- [27] Patient is ~~legally~~ or mentally incapacitated.

Protocol Section 6.5. Concomitant Therapy

Use of any investigational treatment other than lasmiditan is prohibited for the duration of a patient's participation in the study from Screening/Visit 1 through EoS.

Lasmiditan should be used with caution if administered with alcohol or other central nervous system (CNS) depressants; medications that increase serotonin, and medications that lower heart rate.

Concomitant use of lasmiditan and drugs that are P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) substrates should be avoided.

Protocol Section 8.3.1. Serious Adverse Events

Study site personnel must alert Lilly or its designee of any SAE without any delay (and no later than ~~within~~ 24 hours) from the time of investigator awareness of the event via a sponsor approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF.

10.6. Appendix 6: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addition or dependence
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
authorized IMP	a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BP	blood pressure
CONSORT	Consolidated Standards of Reporting Trials
C-CASA	Columbia Classification Algorithm of Suicide Assessment
C-SSRS	Columbia-Suicide Severity Rating Scale
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019

CRF	case report form
clinical research physician	Individual responsible for the medical conduct of the study. Responsibilities of the clinical research physician may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
DMC	data monitoring committee
CCI	
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EoS	End-of-Study
GCP	good clinical practice
GDPR	EU General Data Protection Regulation
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
Informed consent	A process by which a participant 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
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	investigational review board
IWRS	interactive web-response system
LTN	lasmiditan
MedDRA	Medical Dictionary for Regulatory Activities
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication’s labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
NIMH	National Institute of Mental Health
PedMIDAS	Pediatric Migraine Disability Assessment Scale
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetics
PR	pulse rate
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.
SoA	Schedule of Activities
SUSARs	Suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.

TASA	Treatment of Adolescent Suicide Attempters
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.
TOC	Table of Contents
ULN	upper limit of normal

10.7. Appendix 7: Allowable Changes to Study Procedures due to Significant Environmental Regional Disruption

There may be times of exceptional circumstances, such as pandemics or natural disasters, which may cause disruptions to the conduct of the study, specifically to the ability of participants to attend onsite visits as scheduled. Written permission from the sponsor is required prior to implementing procedures outlined in this appendix. The changes to procedures documented in this appendix are temporary measures intended to be used as permitted by local regulation, only during periods of local restrictions. Once restrictions are no longer present, the sites should discontinue the use of these mitigations and return to the standard implementation of the study as outlined in the main protocol.

In such a situation, please follow the guidance below:

- 1) For each visit, sites will document how visit was conducted (telephone, virtual, or onsite), to allow description of changes to study conduct due to significant environmental disruption.
- 2) Patients should complete Visits 1, CCI 7, or early discontinuation in person, as specified in the SoA (Section 1.3). Patients have up to █ days to complete Visit 1, and up to █ days to complete Visits CCI 7, or early discontinuation, per the SoA. However, as specified in the note to the SoA, if extenuating circumstances prevent conduct of in-person visits, the Lilly clinical research physician (CRP) or designee can extend the allowable window to conduct these visits in full.

Note: Sites should make every attempt to schedule patient visits within the defined window. Exceptions to these windows may be granted under certain circumstances with prior approval of the Lilly CRP or designee.

- 3) As long as reasonable attempts to comply with study procedures are made, missing a visit due to these circumstances is not a protocol deviation, and not a reason to discontinue patients.
- 4) As detailed below, there is opportunity to conduct remote visits for Visits CCI █ with a limited set of study procedures, with study patients and an adult parent/guardian. Remote visits can be conducted using video conferencing technology (virtual), if available, or by telephone interview only. The following applies to all remote visits:
 - Timeline for completion should be based on original study schedule, and not on prior visit, if prior visit window was extended due to environmental disruption.
 - Generally, changes in study conduct described in this addendum will not be considered protocol deviations. However, errors in execution of abbreviated remote visit procedures can result in protocol deviations. If sites are required to utilize the procedures in this appendix, they should consult with their monitor and the sponsor to plan and execute the remote visit procedures correctly.

- Patients and parent or guardians should be present for all remote visit procedures. Parent/guardian support and assistance in responding to assessments should follow same guidelines as provided for in-person visits.
- Investigational product and CCI will be dispensed after completion of remote visit procedures. The assumption is that in-person site contact is not possible if the remote visit is being utilized. Depending on local restrictions, dispensed investigational product and CCI can be delivered to the patient via mail, or through some other method that involves limited contact (such as picking up curbside, or from front desk of site), without additional in-person assessments. If possible, unused investigational product and completed CCI can be turned into the site at this time as well. Otherwise, patients will be instructed to retain them to return to the site at the next possible in-person visit. Sites should make every effort to obtain unused investigational product and completed CCI.
 - For IWRS, when in-person weight is not available, sites will use the weight obtained at the most recent in-person study visit to dispense new study medication.
- Sites to collect information regarding AEs (Health Log), concomitant medications (Medicine Log), and treatment and efficacy outcomes (Migraine Treatment Log) during the remote visit. Patients (and parent/guardian if necessary) will use the appropriate section in the CCI to report information to sites; sites will create a secondary source document by capturing the information as provided. Sites should verbally confirm with patient and parent/guardian that investigational product supply corresponds to record of dosing with lasmiditan. For girls of childbearing potential, pregnancy tests should be administered using a home kit, with verbal confirmation of negative test by parent or guardian during the remote visit. In the event of a positive urine pregnancy test during remote visit procedures, patient must be discontinued from investigational product until a serum pregnancy test can be conducted.
- Site personnel should administer all assessments verbally and document the person who administered the assessments, the date and time they were administered, and that they were collected via remote visit. Training requirements for administration of scales (for example, C-SSRS) are not waived for remote visits. For patient-reported outcome assessments (PedMIDAS and health care resource utilization), the site should administer the assessments over the phone reading the questions to patients verbatim (no additional guidance should be offered) in the patients' native language and record answers on behalf of patients into the CRF. The interviewer should receive a verbal confirmation for each response from the person on the phone.

Visit ^{CC} (Enrollment) Remote Visit.**Schedule of Activities for Remote Enrollment Visit**

	CC		Notes	Remote Visit Notes
Visit				
Target Interval Since Previous Visit (Days)				
Procedure/Assessments				
Confirmation of study eligibility	X		Review lab results and confirm study eligibility prior to randomization.	Conducted by investigator prior to remote visit.
Randomization	X			Conducted by investigator prior to remote visit.
Study medication dispensed	X		Study medication can be dispensed in between scheduled visits as needed; not to exceed dosage needed to treat ^{CC} migraine attacks ^{CC} .	Mailed to patient or limited-contact pickup arranged, after completion of remote visit procedures.
Study procedures training	X		Site to instruct patient and parent/guardian on study procedures, including administration of study IP and completion of ^{CC} entries logs.	Conducted during remote visit.
CC				
Concomitant medications (Medicine Log)	X		Collected and captured verbatim at Visit 1; captured in ^{CC} and reviewed at all other visits, including unscheduled study visits, if they occur.	Participants and parent/guardian will use the ^{CC} to report information; sites will create a secondary source document to capture data.
Adverse events (Health Log)	X		Collected and captured verbatim at Visit 1; captured in ^{CC} and reviewed at all other visits, including unscheduled study visits, if they occur.	Participants and parent/guardian will use the ^{CC} to report information; sites will create a secondary source document to capture data.
CC				

Abbreviation: IP = investigational product.

Visit ^{CC} or Visit ^{CC} Remote Visit.**Schedule of Activities for Remote Visit ^{CC} or Visit ^{CC}**

	CC		Notes	Remote Visit Notes
Visit				
Target Interval Since Previous Visit (Days)				
Procedure/Assessments				
Menstrual status	X	X		
Study medication dispensed	X	X	Study medication can be dispensed in between scheduled visits as needed; not to exceed dosage needed to treat ^{CC} migraine attacks ^{CC} .	Mailed to participant or limited-contact pickup arranged, after completion of remote visit procedures.

	CCI		Notes	Remote Visit Notes
Visit				
Target Interval Since Previous Visit (Days)				
Study procedures review	X	X	Site to review study procedures with patient and parent or guardian as needed.	Conducted during remote visit.
Study medication collected	X	X	Returned IP reconciled with dose events captured in CCI.	Returned to site at time new medication is dispensed, or at the next in-person visit.
CCI				
Concomitant medications (Medicine Log)	X	X	Collected and captured verbatim at Visit 1; captured in CCI and reviewed at all other visits, including unscheduled study visits, if they occur.	Patients and parent/guardian will use the CCI to report information; sites will create a secondary source document to capture data.
Adverse events (Health Log)	X	X	Collected and captured verbatim at Visit 1; captured in CCI and reviewed at all other visits, including unscheduled study visits, if they occur.	Patients and parent/guardian will use the CCI to report information; sites will create a secondary source document to capture data.
Treatment with lasmiditan and efficacy outcomes (Migraine Treatment Log)	X	X	Captured in CCI.	Patients and parent/guardian will use the CCI to report information; sites will create a secondary source document to capture data.
CCI				
Clinical Laboratory Tests				
Pregnancy test for females of childbearing potential	X	X	Urine pregnancy test. A positive urine test must be followed by a serum pregnancy test for confirmation.	To be completed at home, using home kit. Parent or guardian to verify result. If positive, patient will be discontinued from IP until serum pregnancy test can be completed.
Scales & Questionnaires				
PedMIDAS	X	X	Self-administered by patient and parent or guardian.	Questions should be read verbatim and responses captured verbatim as reported by the patient. All assessment results should be entered into the CRF.
C-SSRS Since Last Visit – Children’s Version	X	X	Adapted for the assessment of the ideation and behavior categories only (Intensity of Ideation and Lethality of Behavior sections removed). The C-SSRS will be administered by trained site staff to patients ≥7 years old.	Interview conducted by trained administrator. All assessment results should be entered into the CRF.
Self-Harm Supplement Form	X	X		
Self-Harm Follow-Up Form	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.	

	CCI		Notes	Remote Visit Notes
Visit				
Target Interval Since Previous Visit (Days)				
HCRU (recall period “since your last visit”)	X	X	Administered by site staff.	All assessment results should be entered into the CRF.
Assessment of Driving Accidents/Violations – Since Last Visit	X	X	Administered by site staff to patients who are of legal age to drive, per local regulations.	All assessment results should be entered into the CRF.

Abbreviations: CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; HCRU = health care resource utilization; IP = investigational product; PedMIDAS = Pediatric Migraine Disability Assessment Scale; PedsQL = Pediatric Quality of Life Inventory.

10.8. Appendix 8: Protocol Amendment Summary

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [b]: 07 August 2020

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

This amendment provides additional detail on trial execution in the event of significant environmental disruption at investigator sites, detailing procedures that will assure the safety of trial participants and minimize risk to trial integrity during these events.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Clarified participants will be stratified at time of screening.	Minor clarification based on site feedback.
1.3 Schedule of Activities	Increased target interval window to CCI days.	Minor change for added participant flexibility.
1.3 Schedule of Activities	Reorganized Schedule of Activities to group all activities related to CCI in one location. Added specific rows to detail CCI activities.	Minor clarification.
1.3 Schedule of Activities	Added row for confirmation of study eligibility, when dispensing the CCI, treatment with lasmiditan, efficacy outcomes (Migraine Treatment Log), and CCI collection.	Minor clarification added for sites.
1.3 Schedule of Activities	Clarified administration of investigational product and completion of CCI entries are included in study procedure training.	Minor clarification.
1.3 Schedule of Activities	Detailed collection method for PedMIDAS, C-SSRS, Cogstate Brief Battery, PedsQL 4.0 Generic Core Scales, health care resource utilization, and Assessment of Driving Accidents/Violations.	Minor clarification.
5.1 Inclusion Criteria	Clarified inclusion of participant age at the time of screening.	Minor clarification.
8.1.1 Participant CCI	Added instructions for participants less than 12 years of age or adolescents deemed necessary as well as site review of participant CCI.	Added for site clarification.
8.1.1.1 Pain Severity	Clarified definition of pain freedom and pain relief.	To align to the primary analysis in the SAP.
8.2.1 Patient CCI	Added instructions for site review of participant CCI.	Added for site clarification.

Section # and Name	Description of Change	Brief Rationale
8.10.1 Pediatric Migraine Disability Assessment Scale	Clarified the administration method of the scale.	Minor clarification.
8.10.2 Pediatric Quality of Life Inventory™	Clarified the administration method and instructions of the scale for each age group.	Minor clarification.
8.10.3 Health Care Resource Utilization	Clarified the instructions for site personnel when asking questions of the participants.	Minor clarification.
9.4.5.2 Extent of Exposure	Clarified when extent of exposure will be summarized quarterly CCI and 12 months.	Minor clarification to align with other documents.
CCI		
9.4.6.1 Secondary Endpoints	Updated summaries will also be presented by quarter.	To align with objectives and the SAP.
9.4.6.1 Secondary Endpoints	Added text regarding additional analyses for pain freedom in only those attacks treated when pain was moderate to severe.	Minor clarification.
10.6 Appendix 6: Allowable Changes to Study Procedures due to Significant Environmental Regional Disruption	Added appendix outlining allowable changes to study procedures due to significant environmental regional disruption.	Added appendix outlining allowable changes to the study procedures for public health crisis like the Coronavirus disease 2019 (COVID-19) pandemic, a natural disaster, or other significant instability in a region making usual routines dangerous or unpredictable.
Throughout	Other minor editorial changes were made to add clarity.	

Amendment [a]: (03/09/2020)**Overall Rationale for the Amendment**

Protocol H8H-MC-LAHW A Phase 3, 12-Month, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine - PIONEER-PEDS2 has been amended.

The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Modified protocol to add specific information on enrollment
- Clarified justification dose by removing equivalent wording throughout protocol
- Adjusted dose regimen
- Clarified urine drug test
- Changed minor grammatical and formatting error

Section # and Name	Description of Change	Brief Rationale
Table of Contents	Adjusted to incorporate changes	Clarified original intent
Section 1.1, Protocol Summary	Removed with and without aura wording	Clarified original intent
Section 1.3, Schedule of Activities	Vital Signs, Height/Weight Enrollment added	Added for consistency across study visit procedures and to provide most current weight at time of IP dispensing
Section 4.1, Overall Design	Removed with and without aura wording	Clarified original intent
Section 4.1.4, End of Study	Clarified End-of-Study visit	Clarified original intent
Section 4.3, Justification for Dose	Clarified CCI doses; Added sentence to refer to table LAHW	Clarified original intent
Section 5.1, 5.2, Inclusion and Exclusion Criteria	Revision of criteria #7, #8, and #22	Minor revision to improve comprehension; no change to content
Section 6.1, Study Intervention(s) Administered	Provided additional information regarding dosing regimen CCI	Provided full detail on dosing regimen CCI based on completed Study LAHX and modeling and simulation study

Section 6.6, Dose Modification	Added reference to Table LAHW.1	Clarified original intent
Section 7.1, Discontinuation of Study Intervention	Positive result on urine drug screen	Added positive results on urine drug screen as a potential reason for discontinuation
Section 7.2, Participant Discontinuation/Withdrawal from the Study	Early discontinuation visit within CC days	Clarified original intent
Section 8.2.10, Puberty and Menstrual Status	Pubertal status to be determined by blood hormone levels	Clarified original intent
Section 9.5, Interim Analyses	Removed unblinding wording	Clarified original intent
Section 9.5.1, Data Monitoring Committee	Removed cohort wording	Clarified original intent
Appendix 3: Sampling Summary	Values changed for Screening Tests for Planned Total amount from 7.5 to 12.0 Changed Standard Laboratory tests Maximum Number of Samples from 12 to 10 and changed Planned Total amount from 30.0 to 25.0. Added Gonadal Hormones sampling and values	Clarified original intent
Appendix 5: Abbreviations	Removed Companion diagnostic; removed dose from lasmiditan, added a few abbreviations	Clarified original intent; corrections
References	Adjusted 2 References; deleted 1 Reference	Corrections

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Approval	PPD	
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