Protocol H8H-MC-LAHV(c)

Pediatric Options for Migraine Relief: A randomized, double-blind, placebo-controlled study of lasmiditan for acute treatment of migraine: PIONEER-PEDS1 Study.

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Pediatric Options for Migraine Relief: A Randomized, Double-Blind, Placebo-Controlled Study of Lasmiditan for Acute Treatment of Migraine: PIONEER-PEDS1

EudraCT: 2019-004378-24

EU trial number: 2023-506253-38-00

Confidential Information

Lasmiditan (LY573144)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

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

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	*22-Jun-2023*
Amendment (a)	*09-Mar-2020*
Original Protocol	*02-Dec-2019*

Amendment [c]

This is a nonsubstantial amendment.

Overall Rationale for the Amendment:

The rationale for this amendment is to remove the information related to the interim futility analysis as per US FDA request.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Removed the statement on interim futility analysis under statistical analysis.	As per US FDA request.
7.2.1 Discontinuation of Inadvertently Enrolled Patients	Deleted this section.	Per Lilly template update.
9.4.6. Data Monitoring Committee	Previously described process of interim futility analysis conduct and the roles of the SAC and DMC was removed.	As per US FDA request.
9.4.6. Data Monitoring Committee	Added the statement 'Moreover the study will not be stopped for positive efficacy results nor will it be stopped for futility; hence, no alpha will be spent.'	As per US FDA request.
9.5. Interim Analyses	Added the statement 'the study will not be stopped for positive efficacy results nor will it be stopped for futility; hence, no alpha will be spent.' Previously added subsection 9.5.1 *Futility Analysis* was removed.	As per US FDA request.
11. References	Removed a reference (Mehta and Pocock 2011).	Due to removal of subsection 9.5.1 *Futility Analysis*
Throughout the protocol	Minor formatting and editorial changes.	Minor, therefore, not detailed.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

Pediatric Options for Migraine Relief: A randomized, double-blind, placebo-controlled study of lasmiditan for acute treatment of migraine: PIONEER-PEDS1 Study.

Regulatory Agency Identifier Number(s)

EudraCT: 2019-004378-24

EU trial number: 2023-506253-38-00

Rationale:

Migraine is one of the most common neurological conditions in pediatrics. In a large review of 35 population-based studies, the overall prevalence of migraine in children and adolescents (less than 20 years old) is 7.7% (95% confidence interval = 7.6 to 7.8; Abu-Arafeh et al. 2010). Migraine occurs more frequently in adolescents compared with the younger pediatric age groups. There is a significant increase in migraine incidence in females after puberty. In children and adolescents, headache and migraine can result in missed school days (Stang and Osterhaus 1993; Kabbouche and Gilman 2008) and poorer academic performance (Rocha-Filho and Santos 2014). Childhood migraine also has a negative impact on quality of life (Powers et al. 2003; Hershey et al. 2004). There are few treatments approved for the acute treatment of migraine in adolescents, and only one treatment approved for children aged 6 to 11 years. Thus, there remains a significant unmet need for the acute treatment of migraine in children and adolescents.

Lasmiditan is a high-affinity, centrally penetrant, selective 5-hydroxytryptamine (serotonin) 1F (5-HT_{1F}) receptor agonist without significant pharmacological activity at 5-HT_{1B} or 5-HT_{1D} receptors. Evidence suggests that lasmiditan exerts its therapeutic effects by decreasing neuropeptide release and inhibiting pain pathways, including the trigeminal nerve, without causing vasoconstriction in coronary/meningeal arteries.

In adults with migraine with or without aura, lasmiditan 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). Lasmiditan has also been generally well-tolerated in adult studies; the most common adverse events (AEs) reported are generally mild-to-moderate in severity and include

- dizziness
- paresthesia
- somnolence
- fatigue, and
- nausea.

Study H8H-MC-LAHV (Study LAHV) will enable a clinical assessment of lasmiditan in a pediatric patient population with migraine for which the medical need is substantial. This study

is part of a pediatric clinical program that is intended to provide pivotal efficacy and safety data to support use of lasmiditan for acute treatment of migraine in pediatric patients.

The primary objective of Study LAHV is to test the hypothesis that lasmiditan 200 mg is superior to placebo in the proportion of patients at least 6 to less than 18 years of age with pain freedom at 2 hours after dosing. Key secondary objectives are to test whether lasmiditan 100 mg and lasmiditan 50 mg are superior to placebo in the proportion of patients at least 6 to less than 18 years of age with pain freedom at 2 hours. A complete list of study objectives can be found in Section 3. Monitoring and assessment of safety and tolerability in the pediatric population is summarized in Sections 8.2 and 8.3.

Summary of Study Design:

Study LAHV is a multi-country, randomized, double-blind, parallel group, placebo-controlled trial in patients of at least 6 to less than 18 years of age who meet International Classification of Headache Disorders criteria for a diagnosis of migraine. Study LAHV will assess the efficacy, safety, and tolerability of lasmiditan 50 mg, 100 mg, and 200 mg compared to placebo in the treatment of a single migraine attack. Patients will treat a single migraine attack in 2 stages: a double-blind placebo challenge (Stage 1) prior to randomization in the efficacy analysis period (Stage 2).

Patients will record characteristics of treated migraine and outcomes in CCI [redacted] prior to dosing and at specified intervals after dosing. Patients will record any AEs and concomitant use of medication throughout the Treatment Period in CCI [redacted].

An End-of-Study Visit will be conducted within CCI [redacted] days of dosing of study medication or after CCI [redacted] weeks if no migraine attack is treated with study drug.

Study Population

In general, participants may take part in the study if they

- have a history of migraine with or without aura as defined by International Headache Society International Classification of Headache Disorders, 3rd Edition (ICHD-3) (ICHD-3 2018) diagnostic Criteria 1.1 or 1.2.1 and meet the following criteria:
    - history of migraine attacks for more than 6 months
    - report at least 2 and no more than 8 moderate-to-severe migraine attacks per month in the 2 months prior to screening visit
    - duration of a typical untreated migraine attack (excluding sleep) is greater than or equal to 3 hours, and
    - have not, by history, experienced satisfactory response with a previous migraine therapy, in the opinion of the investigator
- can swallow a tablet, and
- weigh at least 15 kg.

For participants taking migraine preventive medication, treatment regimen is stable and has been taken for at least 3 months prior to screening.

In general, participants may not take part in the study if they

- are pregnant or nursing
- have any acute, serious, or unstable medical condition, and
- are actively suicidal or at significant risk for suicide, in the opinion of the investigator.

Number of Participants:

The study will enroll approximately CCI children and adolescents to achieve the desired sample size of CCI patients of at least 6 to less than 18 years of age in the efficacy analysis population.

The evaluable sample will include a distribution that includes at least CCI% children aged 6 to less than CCI (~CCI patients), and at least CCI% adolescents aged CCI to less than 18 (~CCI patients). Within the adolescent population, a similar number will be aged CCI and CCI years. At minimum, at least CCI% will be male (~CCI patients).

Intervention Groups and Duration:

Dosing will be based on weight at screening (Visit 1) to achieve exposures equivalent to 50 mg, 100 mg, and 200 mg in adults (referred to throughout as lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg). In Stage 1, patients will be randomized to receive placebo or lasmiditan 100 mg. CCI [redacted] will be randomized to receive lasmiditan 50 mg, 100 mg, and 200 mg or placebo in Stage 2 (disposition of all other patients detailed in Table LAHV.1).

Each patient's study participation will consist of

- a Screening Visit
- a Study Enrollment Visit
- a Treatment Period of up to CCI weeks in which the patient will be asked to treat a single qualifying migraine attack and complete outcome assessments, and
- an End-of-Study Visit within CCI days of treating a single migraine attack or after completion of Treatment Period without dosing.

Ethical Consideration of Benefit/Risk

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with lasmiditan are justified by the anticipated benefits to participants with migraine.

Statistical Analysis:

The primary efficacy analysis will test the hypothesis that lasmiditan 200 mg is superior to placebo in the proportion of patients who are pain free at 2 hours after dosing in Stage 2 for the efficacy analysis population. Patients randomized to lasmiditan and patients who are CCI [redacted] in Stage 1 are not included in the efficacy analysis population. All patients who receive at least 1 dose of study medication in Stage 1 or Stage 2 will be included in the safety population.

Logistic mixed-effects regression modeling adjusted for CCI [redacted]

CCI [redacted] will be utilized to analyze the primary efficacy end point, where available observed data from all patients at all time points up to 2 hours after dosing will be used to simultaneously estimate treatment effects for lasmiditan (50 mg, 100 mg, or 200 mg) at the 2-hour time point. Logistic modeling will be used to analyze all secondary endpoints except for time to use of additional migraine medication, which will be assessed using a Kaplan-Meier analysis and a log-rank test stratified by CCI [redacted].

Treatment group comparisons for analyses relating to AEs will be assessed using exact Cochran-Mantel-Haenszel tests stratified by CCI [redacted] across all patients and Fisher's exact tests within each age group. Descriptive statistics will be used to summarize

- patient disposition
- patient characteristics
- concomitant therapy, and
- all safety endpoints other than AEs.

Subgroup analyses by age group will be conducted for all efficacy and safety endpoints, and additional subgroup analyses will be conducted for the primary efficacy end point.

A data monitoring committee will monitor the overall safety of this trial by conducting unblinded data reviews. Additional unblinded analyses may be conducted in support of regulatory submissions, if necessary.

1.2. Schema

Illustration of study design for Clinical Protocol H8H MC LAHV.

1.3. Schedule of Activities

	Screening*	Enrollment	Treatment Period	End-of-Study	ED	Notes
Visit	**1**	**2**	**3****	**801**		
Target interval since previous visit	**N/A**	CCI				Site should schedule next visit for earliest possible date. Patients have up to CCI weeks to treat a single migraine attack as an outpatient. End-of-study visit to be scheduled after treatment of a single migraine attack or after completion of Treatment Period without dosing.
Assessments and Procedures						
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	X				
Demographics	X					
Physical examination	X			X	X	Complete physical examination, excluding pelvic and rectal examination.
Vital signs	X			X	X	
Height/weight	X			X	X	
Medical history	X					Includes migraine history.
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	
Migraine treatment history	X					
Concomitant medications	X	X	X	X	X	In addition, to be completed at unscheduled study visits, if they occur.
Adverse events		X	X	X	X	In addition, to be completed at unscheduled study visits, if they occur.
Confirmation of study eligibility		X				
Randomization		X	X			If indicated, randomization for Study Period 2 will occur during treatment of a qualifying migraine attack.
Study medication dispensed		X				Study drug defined as blinded study medication; dispensed by site personnel.
CCI and study procedures training/practice		X				Instructions for study procedures and identification of qualifying migraine, dispensing and training on use of CCI.
PedMIDAS	X					
Cogstate Pediatric Brief Battery	X	X				Participants will be instructed on use at screening. Two training tests to be completed at Visit 1; baseline assessment at Visit 2.

	Screening*	Enrollment	Treatment Period	End-of-Study	ED	Notes
Visit	**1**	**2**	**3****	**801**		
Target interval since previous visit	**N/A**	CCI				Site should schedule next visit for earliest possible date. Patients have up to CCI weeks to treat a single migraine attack as an outpatient. End-of-study visit to be scheduled after treatment of a single migraine attack or after completion of Treatment Period without dosing.
C-SSRS Baseline Screening - Children's Version	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 to patients ≥7 years old.
C-SSRS Since Last Visit – Children's Version		X	X (see note)	X	X	This administration triggered only by spontaneously reported event.
Self-Harm Supplement Form	X	X	X (see note)	X	X	This administration triggered only by spontaneously reported event.
Self-Harm Follow-Up Form	X	X	X	X	X	Required if triggered by the Self-Harm Supplement Form per instructions.
Assessment of Driving Accidents/Violations – Since Last Visit				X	X	Administered by site to patients who are of legal age to drive, per local regulations.
Study medication administered			X			Patients take up to 2 doses of study medication during Treatment Period. Study medication administered by patient or by parent/guardian to patient
CCI						
Study medication collected				X	X	
Clinical Laboratory Tests						
Hematology	X			X	X	
Clinical Chemistry	X			X	X	
Urinalysis	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	Serum pregnancy test at screening. Urine pregnancy test at all other visits. A positive urine test must be followed by a serum pregnancy test for confirmation.
Gonadal hormones	X					Estradiol (females) or testosterone (for males) will be collected for the assessment of pubertal status. Not required to evaluate enrollment eligibility.
Urine drug screen	X					For patients aged ≥ 10 years.
CCI						

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; CCI ; CCI ; ED = early discontinuation; ERB = ethical review board; N/A = not available; PedMIDAS = Pediatric Migraine Disability Assessment Scale.

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 or designee

* Screening evaluations may be repeated once if necessary.

** CCI

2. Introduction

2.1. Study Rationale

Study H8H-MC-LAHV (Study LAHV) will enable a clinical assessment of lasmiditan in a pediatric patient population with migraine for which the medical need is substantial. This study is part of a pediatric clinical program that is intended to provide pivotal efficacy and safety data to support use of lasmiditan in child and adolescent patients with migraine. Study LAHV will assess the efficacy of lasmiditan compared with placebo for the treatment of a single migraine attack. Dosing will be based on weight to achieve exposures equivalent to 50 mg, 100 mg, and 200 mg in adults (referred to throughout as lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg; see Section 6.1). Patients who complete Study LAHV may be eligible to participate in a 1-year open-label safety study of lasmiditan in pediatric patients with migraine.

2.2. Background

Migraine in children and adolescents

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 attacks are characterized by intense pain and associated symptoms, resulting in substantial negative impacts on daily life. While migraine in the pediatric population is similar in nature to adult migraine, it can include

- shorter attacks
- different location of pain, and
- reduced ability to describe associated symptoms.

In children and adolescents, migraine can have a negative impact on function (including missed school days and poorer academic performance) 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, allowing the child to resume normal activities. There are few positive trials of acute medication for the treatment of migraine in children, particularly in the population less than [redacted] years old. High placebo response rates, as well as shorter attack length in this population, have complicated efforts to demonstrate efficacy of treatments (Lewis and Pearlman 2006; Lewis et al. 2005; Tfelt-Hansen et al. 2012; Sun et al. 2013).

Treatment for children and adolescents

Although there have been advancements in options for the pharmacological management of pediatric migraine, current treatments have limitations. Abortive over-the-counter medications are first-line treatments for pediatric migraine attacks but are most effective in mild-to-moderate attacks, and when treatment is initiated early in the attack. Ibuprofen and, to a lesser extent, acetaminophen, have been demonstrated to be effective in children and adolescents (Hämäläinen et al. 1997; Lewis and Winner 2006; Khrizman and Pakalnis 2018).

In more severe cases, approved triptans can be used. Seven 5-hydroxytryptamine (serotonin) 1B/D (5-$HT_{1B/D}$) receptor agonists, collectively known as the triptans, are approved for the treatment of migraine attacks in adults worldwide. In the US, 3 of these are now indicated in the pediatric population (Richer et al. 2016):

- oral rizatriptan
- oral almotriptan, and
- zolmitriptan nasal spray formulation.

Of these, rizatriptan is approved for children and adolescents aged at least 6 to less than 18 years old, while the others are approved for adolescents 12 to less than 18 years old. An additional triptan combination product, oral sumatriptan plus naproxen, is also approved for adolescents 12 to less than 18 years old in the US. Oral almotriptan is also approved for adolescents (12-17 years) in Canada, and nasal sumatriptan has been approved for adolescents (12-17 years) by the EMA. These products are primarily used in moderate-to-severe headaches or after the failure of over-the-counter analgesics and are associated with pain freedom rates of 24% to 41% at 2 hours in pediatric populations (Linder et al. 2008; Zomig® prescribing information 2013; Maxalt® prescribing information 2019; Naproxen-Sumatriptan combination prescribing information 2016). While considered generally safe and efficacious, they are also associated with an increase in nonserious AEs such as

- taste disturbance
- nasal symptoms
- dizziness
- fatigue
- low energy
- nausea, or
- vomiting (Patniyot and Gelfand 2016).

Even with appropriate treatment, approximately one third of pediatric patients remain refractory (El-Chammas et al. 2013). This is concerning, as poor response to therapy is associated with a higher risk of increasing frequency of headaches in adults (Lipton et al. 2015). A retrospective, observational study across 4 states found that 46% of pediatric patients with migraine are not prescribed or recommended medication, while 84% are not prescribed or recommended evidence-based medication (Nicholson 2015). Headache is a common reason for children and adolescents to visit the emergency department, with national estimates of 250,000 visits occurring annually (Kedia et al. 2014). Therefore, there is a need for additional safe and effective medications for the acute treatment of children and adolescents with migraine.

Pathophysiology of a migraine and lasmiditan

Early theories attributed the pathophysiology of migraine to vasodilation of intracranial vessels (Humphrey et al. 1990; Sprenger and Goadsby 2009; Mitsikostas and Tfelt-Hansen 2012). The desire to develop effective migraine treatments without vasoconstrictive properties led to the discovery of selective 5-HT_{1F} receptor agonists and other molecules (Sprenger and Goadsby 2009; Neeb et al. 2010; Xavier et al. 2017). In the current neurogenic

theory of the pathophysiology of migraine, migraine attacks are thought to be explained by activation of trigeminal system 5-HT_{1F} receptors (Ramadan et al. 2003; Capi et al. 2017; Xavier et al. 2017).

Lasmiditan is a novel therapy for the acute treatment of migraine. Lasmiditan is a high-affinity, centrally penetrant, 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). Lasmiditan is structurally and mechanistically distinct from other approaches for the acute treatment of migraine, such as triptans, and lacks the vasoconstrictive effects of triptans that result from 5-HT_{1B} activity.

In 2 placebo-controlled, randomized, Phase 3 efficacy trials of a single migraine attack in adults, lasmiditan 50 mg, 100 mg, and 200 mg were associated with a greater proportion of patients achieving pain freedom and freedom from their most bothersome associated symptom at 2 hours (Kuca et al. 2018; Goadsby et al. 2019). Lasmiditan may provide therapeutic benefit to children and adolescents from at least 6 to less than 18 years of age.

2.3. Benefit/Risk Assessment

Migraine is a disabling and prevalent disorder that impacts children. There are few approved treatments for migraine in children and adolescents in the US, with only 1 approved treatment (rizatriptan) available for children aged at least 6 to less than 12 years. Current treatments are not sufficiently meeting the needs of all patients (El-Chammas et al. 2013). Lasmiditan is a highly selective 5-HT_{1F} agonist that is being developed for the acute treatment of migraine attacks. Lasmiditan demonstrated efficacy and safety in 2 placebo-controlled, randomized, Phase 3 efficacy trials in adults (Kuca et al. 2018; Goadsby et al. 2019). If approved in a pediatric population, lasmiditan would provide another acute treatment option for children and adolescents with migraine.

As a centrally penetrant 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.

It is generally well-tolerated, and the vast majority of events in adults are mild-to-moderate and of limited duration. Further information can be found in the Investigator's Brochure.

Patients who complete visits 1, 2, 3, and 801 in Study LAHV may be eligible to participate in an open-label, 12-month, long-term safety study, Study LAHW. Treatment of a qualifying migraine during the CCI -week Treatment Period is not required to qualify for Study LAHW. In Study LAHW, patients will have the opportunity to treat multiple migraine attacks with lasmiditan.

3. Objectives and Endpoints

The objective of Study LAHV is to evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared to placebo in the acute treatment of migraine in pediatric patients at least 6 to less than 18 years of age. Monitoring and assessment of safety and tolerability of lasmiditan in the pediatric population is summarized in Sections 8.2 and 8.3.

Objectives	Endpoints
Primary	
To test the hypothesis that lasmiditan 200 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients ≥6 to <18 years of age	Proportion of patients ≥6 to <18 years of age with pain freedom at 2 hours after dosing
Key Secondary	
To test the hypothesis that lasmiditan 100 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients ≥6 to <18 years of age	Proportion of patients ≥6 to <18 years of age with pain freedom at 2 hours after dosing
To test the hypothesis that lasmiditan 50 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients ≥6 to <18 years of age	Proportion of patients ≥6 to <18 years of age with pain freedom at 2 hours after dosing
Secondary*	
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to pain freedom in age subgroups	Proportion of patients with pain freedom at 2 hours after dosing in the subgroup of patients ≥6 to CCI years of age and in the subgroup of patients CCI to <18 years of age
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to pain relief	Proportion of patients ≥6 to <18 years of age with pain relief at 2 hours after dosing
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to resolution of the MBS	Proportion of patients ≥6 to <18 years of age MBS-free at 2 hours after dosing
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to absence of individual associated symptoms of migraine	In patients ≥6 to <18 years of age: • Proportion of patients nausea-free at 2 hours after dosing • Proportion of patients photophobia-free at 2 hours after dosing • Proportion of patients phonophobia-free at 2 hours after dosing
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to sustained pain freedom	Proportion of patients ≥6 to <18 years of age with sustained pain freedom at 24 and 48 hours
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to use of additional medication within 24 and 48 hours	In patients ≥6 to <18 years of age: • Proportion of patients using additional medication for migraine within 24 and 48 hours • Time to use of additional migraine medication

Objectives	Endpoints
[redacted]	
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to patient-reported global measure of change	Proportion of patients ≥6 to <18 years of age with PGIC rating of "a lot better," "better," "no different," "worse," and "a lot worse" at 2 hours
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to the degree of migraine interference in normal activities	Proportion of patients ≥6 to <18 years of age with a rating of 0 ("not at all"), 1 ("a little"), 2 ("a lot"), or 3 ("completely") at 2 hours
Acceptability of the Formulation	
To evaluate the acceptability of lasmiditan tablets (50 mg, 100 mg, and 200 mg) with respect to ease of swallowing of the tablets	Proportion of patients ≥6 to <18 years of age with a rating of "very easy," "easy," "neither easy nor hard," "hard," or "very hard" at 24 hours after dosing

Abbreviations: MBS = most bothersome symptom; PGIC = Patient Global Impression of Change.
*Other analyses include analyses by age subgroups for all secondary efficacy and safety endpoints.
Note: Efficacy-related objectives are assessed within the efficacy analysis population.

4. Study Design

4.1. Overall Design

Study LAHV is a randomized, double-blind, placebo-controlled, parallel group study. Patients will complete a double-blind placebo challenge period (Stage 1) in the first CCI of the treated attack, with CCI eligible for randomization into the efficacy analysis period (Stage 2). In Stage 2, the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo will be examined.

4.1.1. Screening

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, respectively). All screening procedures will be performed according to the Schedule of Activities. 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. The duration of the screening Period is up to CCI days.

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 and use of CCI . Patients will be randomized for Stage 1. Study medication for Stage 1 and all potential study medications that may be required for Stage 2 will be dispensed.

Investigators and site staff will educate patients regarding identification of qualifying migraine attacks, including differentiation of migraine attacks from tension headache in those patients who experience both types. Trainings will be provided for

- all procedures for study medication administration
- the use of CCI , and
- documentation of AEs and concomitant medications.

4.1.3. Treatment Period

In the Treatment Period (Visit 3), patients will have up to CCI weeks to treat a single qualifying migraine attack with study medication. Stage 1 treatment occurs in the first CCI of the treated attack. Only CCI will be eligible for randomization into Stage 2. Please see Table LAHV.1 for disposition of other treatment groups.

A qualifying migraine attack meets the following criteria:

- Moderate or severe migraine pain intensity, defined as Faces 3 through 5 on a 5-Face Pain Scale (see Section 8.1.2), for less than 30 minutes.
- Migraine occurs in a setting where study medication can be administered, and study procedures can be followed.

- No administration of medication for acute treatment of migraine pain, or associated symptoms, within the preceding 24 hours.

Migraine attacks that do not correspond to these characteristics may be treated with patient's usual treatment for migraine attacks.

If the patient is CCI years of age or younger, or if deemed necessary for older children, then a responsible adult who has knowledge of the conduct of this study may supervise migraine treatment and study procedures during a qualifying migraine attack. It is the responsibility of the parent or guardian to provide the necessary guidance or training to other responsible adults.

Site responsibilities

While there are no formal site visits during the Treatment Period, sites will maintain contact with the patient and the parent or guardian through regular phone calls (every CCI weeks or until treatment occurs) during the Treatment Period to reinforce instructions regarding conditions for a qualifying migraine attack. Potential questions and issues may be discussed and reviewed. If information is spontaneously reported during those interactions, AE collection may occur. Site personnel should remind the patients and parents or guardians of the study timelines for identification and treatment of a qualifying migraine attack at each interaction.

4.1.3.1. Treatment of Qualifying Migraine

All dosing will occur in the context of a single migraine attack.

1. Patients will utilize the CCI to confirm presence of a qualifying migraine and to record baseline characteristics.
2. Patients will dose with Stage 1 medicine.

CCI after Stage 1 dosing, the patient will report pain status via the CCI . CCI will communicate with the study interactive web-response system (IWRS) and will then provide instructions to the patient regarding further actions. Patient instructions regarding further dosing in Stage 2 will vary depending on response to treatment and randomized group in Stage 1. Table LAHV.1 describes what actions are taken based on response to treatment during Stage 1.

Table LAHV.1. Instructions for Stage 2 by Stage 1 Outcome

CCI

A CCI in Stage 1 will be assigned to receive placebo in Stage 2 in order to maintain the blind, as they have already received a therapeutic dose of active drug. They are not included in the efficacy population.

Patients who do not achieve satisfactory relief of migraine pain or associated symptoms may use additional medication after completion of the 2-hour assessments or any time thereafter if the migraine does not resolve or recurs (see Section 6.5.1).

In order to protect study blinding, further details on randomization and CCI in Stage 1 are provided in the ethical review board (ERB) supplement, and not detailed here.

CCI

If the patient is less than CCI 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. Adults can assist the patient in the reading and comprehension of the CCI or in manual entry of the patient's responses, but should not provide answers for the patient.

CCI

4.1.4. *End-of-Study Visit*

An End-of-Study Visit will be conducted within CCI days of dosing of study medication or after CCI weeks if no attack is treated during the Treatment Period. Patients will be reminded to return any remaining study medication to the clinic, at which time accurate dosing per Stage 2 instructions will be confirmed. CCI will be performed, and vital signs, body weight, and height will be assessed. Study site staff will CCI and record AEs and concomitant medications reported during the Treatment Period.

4.2. Scientific Rationale for Study Design

Patient population

This study will enroll pediatric patients who

- have a history of migraine for at least 6 months
- experience 2 to 8 migraine attacks per month in the 2 months prior to study entry that are generally greater than 3 hours in duration, and
- have not, by history, experienced satisfactory response with a previous migraine therapy, in the opinion of the investigator.

These patients are best able to identify a qualifying migraine attack and to participate in a trial that requires some duration of migraine symptoms in order to assess outcomes at 2 hours postdose. Additionally, as they have not experienced satisfactory relief from a previous treatment, they may benefit from treatment with lasmiditan.

Placebo response

In studies of acute migraine treatments, placebo response rates for 2-hour pain freedom have been shown to be generally higher among pediatric patients compared with adults. In previous parallel-group studies of drugs with US Food and Drug Administration (FDA) pediatric indication for acute treatment of migraine, placebo response rates in the pediatric studies range from 10% to 34%, compared with 1% to 15% in adult patients (pediatric: Winner et al. 2002; Visser et al. 2004; Rothner et al. 2006; Linder et al. 2008; Derosier et al. 2012; Ho et al. 2012; Winner et al. 2016; adult: Dahlöf et al. 1998; Teall et al. 1998; Tfelt-Hansen et al. 1998; Diener et al. 1999; Pascual et al. 2000; Dahlöf et al. 2001; Dowson et al. 2002; Dodick et al. 2005; Brandes et al. 2007).

Primary end point

The primary end point of the proportion of patients with pain freedom at 2 hours is the standard for the assessment of benefits of acute therapy for migraine and represents an outcome that is

desired and valued by patients (Lipton et al. 2002; FDA 2018). Based on the performance in adult efficacy trials, we expect that lasmiditan will demonstrate a meaningful clinical effect within this time frame. Other outcomes will include the effect on associated symptoms of migraine, including

- that identified as most bothersome by patients
- pain relief
- sustained pain freedom, and
- the degree of migraine interference in ability to perform normal activities.

Additional migraine therapy

Patients who do not achieve satisfactory relief of migraine pain or associated symptoms may use additional medication for rescue after completion of the 2-hour assessments, or any time thereafter, if the migraine does not resolve or recurs. Patients who take additional medication for rescue will be classified as CCI in the efficacy analyses. Rescue medication can include patient's usual treatment for acute migraine attack, with the exception of triptans, opiates, barbiturates, and ergotamine derivatives until 24 hours after administration of study medication.

Clinical laboratory procedures

Laboratory procedures are limited to those essential to the protocol objectives. Frequency and number of assessments were assessed to minimize blood volumes based on recommendations for restriction of total blood volumes in pediatric research.

4.3. Justification for Dose

In order to identify the lowest possible dose that provides efficacy in a pediatric population, lasmiditan treatment in Stage 2 will include weight-based doses that correspond to 50 mg, 100 mg, and 200 mg adult exposures (Table LAHV.2 and Table LAHV.3). This is supported by the efficacy, safety, and pharmacokinetic (PK) data described below.

4.3.1. Efficacy and Safety Data

In the pivotal efficacy trials in adults (301/LAHJ and 302/LAHK), all doses of lasmiditan (50 mg, 100 mg, and 200 mg) were superior to placebo for primary and key secondary endpoints of pain freedom and freedom from most bothersome symptom (MBS) at 2 hours. A consistent dose-response relationship was observed with those in higher dose groups having a greater likelihood of response across multiple efficacy endpoints. In addition, a dose response was observed in the proportions of patients reaching pain freedom at each time point through 2 hours in studies 301/LAHJ and 302/LAHK as well as the time when each dose was first statistically significantly different from placebo. The proportion of patients achieving pain freedom was statistically significant compared with placebo at 1 hour for the lasmiditan 200 mg treatment group in both 301/LAHJ and 302/LAHK. The lasmiditan 100 mg treatment group separated from placebo at 1 hour (302/LAHK) or 1.5 hours (301/LAHJ) while the 50 mg group achieved significant pain freedom compared with placebo at 2 hours.

All 3 doses of lasmiditan are generally well-tolerated. Most common AEs were related to the central nervous system activity of lasmiditan and were mild-to-moderate in severity. The general type and nature of TEAEs were similar across dose groups. The frequency of reported TEAEs generally increased in a dose-dependent manner. There was a numerically higher number of patients with at least 1 TEAE in the lasmiditan 200 mg dose group (40.6%) compared with 100 mg (36.2%) and 50 mg (25.4%) dose groups. No individual TEAE met statistical significance from the trend test that compared the 100 mg and 200 mg dose regimens.

4.3.2. Pharmacokinetics

Study LAHX was a Phase 1, multicenter, open-label, single dose study to determine the PK, safety, and tolerability of lasmiditan in pediatric migraine patients 6 to <18 years of age (n=18).

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Following single -dose administration, plasma concentrations peaked at a median t_{max} value of 1.5 to 2 hours postdose and then declined with a geometric mean terminal half-life of approximately 4 hours. This is consistent with the PK previously observed in adults.

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4.4. End-of-Study Definition

A patient will be considered to have completed the study if they have completed Visit 1, Visit 2, Visit 3, and End-of-Study Visit. Patients may have completed the study without treatment of a qualifying migraine with study medication as long as they have completed the full [redacted] weeks of Visit 3 and End-of-Study Visit procedures.

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 for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

Type of patient and disease characteristics

[1] Patient is at least 6 and less than 18 years of age at Screening (Visit 1).

[2] Patient must have a minimum body weight of 15 kg.

[3] Patient has a history of migraine with or without aura as defined by International Headache Society International Classification of Headache Disorders, 3rd Edition (ICHD-3) (ICHD-3 2018) diagnostic criteria 1.1 or 1.2.1 and meets the following criteria:

- History of migraine attacks for more than 6 months
- Reports at least 2 and no more than 8 moderate-to-severe migraine attacks per month in the 2 months prior to Screening Visit
- Duration of a typical untreated migraine attack (excluding sleep) is greater than or equal to 3 hours
- Patient has not, by history, experienced satisfactory response with a previous migraine therapy, in the opinion of the investigator.

[4] Patient must be able to swallow a tablet.

[5] 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

[6] 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.

[7] 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.

[8] 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 partner until 30 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.

[9] 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 been 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, enrollment, or both:

Medical conditions

[10] Patient has a history or clinical evidence of congenital heart disease, suspected or confirmed.

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[12] Within 6 months of screening, patient had

- myocardial infarction
- unstable angina
- percutaneous coronary intervention, or
- coronary artery bypass graft.

[13] Patient has planned cardiovascular surgery or percutaneous coronary angioplasty, or has a history of stroke.

[14] Patient has any liver tests outside the normal range at screening that are clinically significant. Alanine aminotransferase (ALT) >2x upper limit of normal (ULN), or 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's syndrome:

- Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits)
- Absence of liver disease
- ALT, aspartate aminotransferase (AST), and ALP ≤1x ULN at screening, and
- Hemoglobin not significantly decreased at screening.

[15] 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.

[16] Patient is, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

[17] 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.

[18] Patient is pregnant or breastfeeding.

[19] 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

[20] Patient has used opioids or barbiturate-containing analgesic more than 3 times per month for the treatment of pain in more than 2 of the past 6 months.

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

[22] 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

[23] 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.

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

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

Prior/concurrent clinical trial experience

[26] 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.

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

[28] Patient has previously completed or withdrawn from this study or any other study investigating lasmiditan and has previously received the investigational product.

Other exclusions

[29] Patient is legally or mentally incapacitated.

[30] Patient is a child of investigator site personnel directly affiliated with this study, their immediate families, or both. Immediate family, whether biological or legally adopted, is defined as a

- spouse
- parent
- child, or
- sibling.

[31] Patient is a child of Lilly employees.

[32] In the opinion of the investigator or sponsor, patient is unsuitable for inclusion in the study.

5.2.1. Rationale for Exclusion of Certain Study Candidates

Migraine is uncommon in children younger than 6 years of age and is difficult to diagnose in that age group; therefore, studies in children younger than 6 years of age, including neonates, are highly impractical. The safety and efficacy of drugs for the acute treatment of migraine can be

evaluated in pediatric patients 6 to less than 18 years of age. Criteria 1 through 10 define a pediatric population with a history of migraine that is suitable for this study. Criteria 11 to 26 exclude medical conditions, medication intolerance, and concomitant medication use that may confound the assessment of study endpoints. Criteria 27 to 32 prevent conflict of interest in study participants.

5.3. Lifestyle Considerations

Patients will be allowed to consume their usual diet throughout the study period. When treating a qualifying migraine attack, patients will be asked to complete CCI [redacted]. Patients will be asked to remain awake and to prioritize completion of study assessments for about 2.5 hours from administration of study medication. Patients are asked to determine their ability to comply with study procedures before electing to dose a migraine attack with study medication (for example, the time until typical bedtime or scheduled activities that may interfere with ability to complete study procedures). Each patient is allotted a period of CCI [redacted] weeks in order to allow sufficient opportunity to treat a qualifying migraine attack.

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. During the treatment of a qualifying 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.

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 publishing requirements and to respond to queries from regulatory authorities. Minimal information includes

- demography
- screen failure details
- eligibility criteria, and
- any serious adverse event (SAE).

Based on the clinical judgment of the investigator, patients who fail to qualify at Enrollment Visit 2 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 [redacted] 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. If rescreening is performed, the parent or guardian must sign a new ICF, and patient must sign a new assent and will be assigned a new identification number. A patient may undergo a maximum of 2 screening visits for this study (only 1 rescreening visit is permitted).

6. Study Intervention

6.1. Study Intervention Administered

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.

This table lists the interventions used in this clinical study.

Intervention Name	Lasmiditan	Placebo
Dosage Level(s)	Stage 1: 100 mg exposure in a single dose Stage 2: 50 mg, 100 mg, or 200 mg exposure in a single dose	Stage 1: placebo in a single dose Stage 2: placebo in a single dose
Route of Administration	Oral	Oral
Authorized as defined by EU Clinical Trial Regulation	Authorized and not used according to EU authorization (pediatric indication not yet authorized, adult indication authorized)	Not authorized

Packaging and labeling

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

This study involves a comparison of lasmiditan film-coated tablets with placebo. The study medication will be administered by mouth. To maintain the blind, each dose will require [redacted] tablets.

The dose to be administered to each participant, by weight, was determined by PK and safety data from Study LAHX in addition to simulation and modeling (Section 4.3.2). The selected dose for each weight cohort is intended to achieve exposures comparable to the 50 mg, 100 mg, and 200 mg doses of lasmiditan in adults.

No adjustments to dispensed study medication will be made if a patient's weight changes during the study.

Table LAHV.2 and Table LAHV.3 show the planned treatment regimens, by dose, for Stage 1 and Stage 2.

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Placebo and active drug for a particular CCI cohort will be similar in appearance and taste, and the number of tablets of the study medication will be the same for each CCI cohort.

If the patient is less than CCI years of age, or if deemed necessary for older children, the parent or guardian, or another responsible adult, will be asked to 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 the following:

- explaining the correct use of the investigational product to the patient and parent or guardian and site personnel
- ensuring that patients are able to swallow whole tablets
- verifying that instructions for use are followed properly, and
- maintaining accurate records of study medication dispensing and collection, and at the end of the study, returning all unused medication to Lilly or its designee.

6.2. Preparation, Handling, Storage, and Accountability

Study medication will be labeled according to the country's regulatory requirements. The investigator or his or her designee is responsible for the following:

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only participants enrolled in the study may receive study medication and only authorized site staff may supply study medication. All study medication must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance

with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study medication accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study medication are provided in the Pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Treatments will be assigned in a double-blind manner. Details on randomization and definitions of response in the placebo challenge period (Stage 1) will only be located within the ERB supplement. Patients who are CCI after Stage 1 dosing will be randomized in a CCI ratio (placebo: lasmiditan 50 mg: lasmiditan 100 mg: lasmiditan 200 mg) to study treatment in Stage 2. Randomization will be stratified by CCI in Stage 2. Age groups include

- at least 6 to less than CCI years of age, and
- CCI to less than 18 years of age.

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

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

6.4. Study Intervention Compliance

Compliance with dosing instructions will be assessed at the End-of-Study Visit by documentation of returned, unused investigational product. Deviations from the prescribed dosage regimen should be recorded in the electronic case report form (eCRF).

6.5. Concomitant Therapy

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

- any investigational treatment other than lasmiditan.

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. These 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 CCI .

6.6. Dose Modification

Not applicable.

6.7. Intervention after the End of the Study

Patients who complete this study may be eligible to participate in Study LAHW if enrollment criteria for Study LAHW are met. Patients who are not eligible, or who choose not to participate in Study LAHW, will be referred to their local physician or treatment centers for migraine treatment as clinically indicated.

7. Discontinuation of Study Intervention and Participant Discontinuation and Withdrawal

7.1. Discontinuation of Study Intervention

If a patient discontinues prior to dosing with study medication, and before completion of the Treatment Period, early discontinuation procedures will be completed per the Schedule of Activities of this protocol.

7.2. Participant Discontinuation and Withdrawal from the Study

Patients may withdraw from participation at any time during study.

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- pregnancy
- investigator decision
    - if the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires addition of new migraine treatment, or a change in dose of ongoing migraine treatment, discontinuation from the study occurs prior to change in treatment
- sponsor decision
- subject decision, and
    - the patient or the patient's parents or legal guardian withdraws consent from the study.

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of this protocol.

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.

8. Study Assessments and Procedures

The Schedule of Activities 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 4 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 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

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8.1.2. Primary Efficacy Assessment

Pain freedom

The primary end point is the proportion of patients at least 6 to less than 18 years of age with pain freedom at 2 hours, defined as a reduction of baseline pain from moderate or severe (Faces 3 to 5) to no pain (Face 1).

5-Face Pain Scale.

Migraine pain severity will be recorded in CCI using a 5 Face Pain Scale at each assessment time. Migraine pain intensity is defined as follows:

- Face 1 = no pain
- Face 2 = mild pain
- Faces 3 and 4 = moderate pain
- Face 5 = severe pain (Maunuksela et al. 1987).

The patient must select the number corresponding to the face that represents their current pain severity. Response to the 5-Face Pain Scale will also be used for a number of other secondary pain-related assessments.

8.1.3. Secondary Efficacy Assessments

8.1.3.1. Other Pain-Related Outcomes

Migraine pain severity will be recorded using a validated 5-Face Pain Scale at each assessment interval as described in Section 8.1.2. This enables calculation of the following secondary outcomes:

- pain relief, defined as a reduction of baseline pain from moderate or severe (Faces 3 to 5) to mild or no pain (Face 1 or 2) or patient asleep
- pain freedom and pain relief at 30-minute intervals up to 2 hours postdose, and
- sustained pain freedom at 24 and 48 hours, defined as the proportion of patients who are pain free at 2 hours with no use of rescue medication or no relapse within the specified time point (24 or 48 hours) of the initial treatment (Tfelt-Hansen et al. 2012).

8.1.3.2. Associated Symptoms of Migraine

The associated symptoms of migraine will be captured in CCI at each assessment interval. Before dosing, patients 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 to them. The selected symptom will be identified as the MBS for that patient, within that attack.

The MBS is identified as follows:

- For patients who report experiencing more than 1 of these symptoms, CCI prompts them to identify which is the "MBS."
- For patients who report experiencing only 1 of the symptoms, that symptom is automatically identified as most bothersome.
- Patients who report experiencing none of these symptoms are excluded from the MBS analyses.

8.1.3.3. Interference in Daily Activities

A CCI is used to capture the magnitude of migraine interference with normal daily activities with the question: "How much is your migraine stopping you from doing what you usually do, such as play or do schoolwork or other work?" Responses will be recorded on a 4-point numeric rating scale at each assessment time:

- 0 = not at all
- 1 = a little
- 2 = a lot
- 3 = completely.

This 4-point numeric rating scale is consistent with FDA guidance (FDA 2018) on the assessment of symptom severity. Although not formally validated, similar 4-point assessments have been used to assess functional disability in clinical trials and large population studies documented in the migraine literature, including in pediatric populations (Bigal et al. 2007; Derosier et al. 2012; Ho et al. 2012). Global assessment using a single item was preferred for use

in [redacted] to reduce patient burden and to increase the likelihood of obtaining complete patient responses.

8.1.3.4. Patient Global Impression of Change

Patients will be asked to record their Patient Global Impression of Change (PGIC) to the question, "How did the medicine make you feel?" using a 5-point Likert scale (a lot better, better, no different, worse, a lot worse) at 2 hours post dose.

The PGIC is a patient-rated global measure of change (Guy 1976) and represents a global assessment of effects of the study medication on multiple outcomes, including

- migraine pain
- associated symptoms
- side effects, and
- function (Geisser et al. 2010; Scott and McCracken 2015).

8.1.3.5. Additional Migraine Treatment

Use of additional treatment for migraine within 48 hours of treatment will be captured from information reported in the [redacted].

During the treatment of a qualifying migraine attack, the [redacted] will remind patients to record any concomitant medication in the [redacted], including any taken up to 24 hours prior to administration of study medication and in the 48-hours after dosing. The [redacted] will remind patients that additional medication for pain and symptoms of migraine is permitted after completion of 2-hour assessments. See Section 8.2.1 for additional information.

At the End-of-Study Visit, this information will be reviewed, reconciled, and recorded with concomitant medications captured at screening and Enrollment visits.

8.2. Safety Assessments

Safety and tolerability assessments in pediatric patients (6 to less than 18 years of age) will include the following standard assessments as secondary endpoints:

- vital signs including blood pressure (BP), pulse rate (PR), and body temperature
- [redacted]
- AE monitoring
- [redacted]
- assessment of growth including height and weight, and
- suicidality, measured by the C-SSRS-Children's version.

Planned time points for all safety assessments are provided in the Schedule of Activities. Any clinically significant findings from physical examination, [redacted], vital sign measurements, or [redacted] that result in a diagnosis should be reported to Lilly or its designee as an AE via an eCRF.

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.

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During the Treatment Period, patients will be asked to record AEs and concomitant medication use CCI [redacted]. If the patient is less than CCI [redacted] 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 [redacted].

At every Postscreening Visit, site personnel will review the CCI [redacted] with the patient or guardian and record any change in the preexisting condition(s) and any new conditions as AEs. For each AE, investigators should record

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

Site personnel will also record use of concomitant medications, including any additional treatments for migraine. For each concomitant medication, investigators should record via eCRF the

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

8.2.2. Physical Examinations

For each patient, a complete physical examination will be performed at Visit 1 (screening) and at Visit 801 (End-of-Study). 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 body temperature, systolic and diastolic BP, and PR. BP and PR measurements will be taken when the patient is in a sitting position. Blood pressure readings will be collected using the appropriate size pediatric BP cuffs.

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

8.2.5. Clinical Safety Laboratory Assessments

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities. Use of local anesthetics (for example, EMLA cream) consistent with local prescribing information is permitted during the study visit to ease discomfort associated with venipunctures. Investigators must document their review of each laboratory safety report.

8.2.5.1. Hepatic Safety Monitoring

8.2.5.1.1. Close Hepatic Monitoring

Laboratory tests (Appendix 5), including ALT, AST, ALP, TBL, direct bilirubin, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
• ALT or AST <1.5x ULN	• ALT or AST ≥3x ULN
• ALP <1.5x ULN	• ALP ≥2x ULN
• TBL <1.5x ULN	• TBL ≥2x ULN (except for patients with Gilbert's syndrome)
• ALT or AST ≥1.5x ULN	• ALT or AST ≥2x baseline
• ALP ≥1.5x ULN	• ALP ≥2x baseline
• TBL ≥1.5x ULN	• TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

Note: All ULN values should be age adjusted (AAULN)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels. Special care should be taken to minimize the volume of blood taken during hepatic monitoring.

8.2.5.1.2. Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
• ALT or AST <1.5x ULN	• ALT or AST ≥3x ULN with hepatic signs/symptoms[a], or • ALT or AST ≥5x ULN
• ALP <1.5x ULN	• ALP ≥3x ULN
• TBL <1.5x ULN	• TBL ≥2x ULN (except for patients with Gilbert's syndrome)
• ALT or AST ≥1.5x ULN	• ALT or AST ≥2x baseline with hepatic signs/symptoms[b], or • ALT or AST ≥3x baseline
• ALP ≥1.5x ULN	• ALP ≥2x baseline
• TBL ≥1.5x ULN	• TBL ≥2x baseline (except for patients with Gilbert's syndrome)

Note: All ULN values should be age adjusted (AAULN)

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR and direct bilirubin, if total bilirubin was elevated.

Based on the participant's age, medical history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for viral hepatitis A, B, C, E; autoimmune hepatitis; or an abdominal imaging study (for example, ultrasound, MRI, or CT scan). Consider additional tests, based on the medical history and clinical picture, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Special care should be taken to prioritize more pertinent blood tests and minimize the volume of blood taken during hepatic evaluation. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a pediatric hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy as deemed appropriate for the clinical condition and participant's age.

8.2.5.1.3. Additional Hepatic Data Collection

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who meet one or more of the following five conditions:

- elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
  - in participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
- elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
  - in participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
- elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
  - in participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
- hepatic event considered to be an SAE
- discontinuation of study drug due to a hepatic event.

Note: the interval between the two consecutive blood tests should be at least 2 days. All ULN values should be age adjusted (AAULN).

8.2.6. Cognition

At enrollment, cognition will be assessed by the Cogstate Pediatric Brief Battery (© 2018 Cogstate Ltd). This is a brief 15- to 18-minute computerized cognitive assessment 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
- have 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 citation for driving violation, at the End-of-Study Visit to those patients at the legal age of driving, per local regulations.

8.2.8. Suicidal Ideation and Behavior Risk Monitoring

Assessment of suicidal ideation and behavior will be conducted using C-SSRS – Child 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 to be followed.

8.2.8.1. Columbia-Suicide Severity Rating Scale – Child Version

Columbia-Suicide Severity Rating Scale is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire (Posner et al. 2011). The scale was developed by the National Institute of Mental Health trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. The children's version of the C-SSRS will be administered to all patients by qualified site personnel according to the Schedule of Activities (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 have been 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 Schedule of Activities 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 heavy personal items, including large jewelry, wallets, coats, etc.

8.2.10. Puberty and Menstrual Status

Blood hormone levels will be collected at Visit 1. Onset of first menstruation will be assessed (yes/no) at Visit 1 by the investigator, and female patients who have started menstruating will be asked if they are menstruating (yes/no) at the time they dose a qualifying migraine in the e-Diary. 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 with an appropriate health care option in these cases:

- AEs that are serious or otherwise medically important
- AEs that are considered related to the investigational product or the study, or
- AEs 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 CRF, the occurrence and nature of each patient's preexisting 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) and the 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 CRF clarifying, if possible, the circumstances leading to discontinuation of treatment.

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

Serious adverse events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability or incapacity
- congenital anomaly or birth defect
- 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 one 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. AEs that occur during the Treatment Period are tracked by the patient using CCI [redacted] and recorded in the CRF at the End-of-Study Visit. 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 9.4.4) 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 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 patients once they have discontinued 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 patient 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. Suspected Unexpected Serious Adverse Reactions

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

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 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 greater than 400 mg in a 24-hour period. Doses exceeding the maximum therapeutic dose may be associated with increased incidence, severity of AEs, or both; 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

This section is not applicable for this study.

8.8. Biomarkers

This section is not applicable for this study.

8.9. Immunogenicity Assessments

This section is not applicable for this study.

8.10. Medical Resource Utilization and Health Economics

The self-reported questionnaires will be administered according to the Schedule of Activities 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 at screening. 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 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.

Higher values are indicative of a greater level of disability due to headache. This instrument is considered reliable and valid (Stewart et al. 1999; Hershey et al. 2001).

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

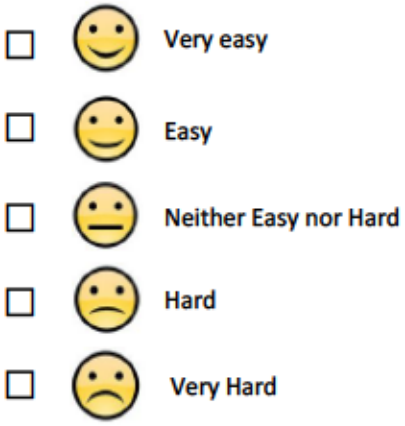
- On how many days in the last 3 months did you have a headache?
  On a scale of 0-10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be).

8.10.2. Acceptability of Tablet

The assessment of acceptability of the lasmiditan oral formulation (single tablet) will be collected for all patients at the 24-hour assessment in CCI .

The patient will be asked to provide responses to a question designed to assess the patient's ability to swallow the tablet. The scale includes both a hedonic and Likert-type response scale to assist children and adolescents in providing a response to the following:

"Think about the experience of swallowing the study medicine. How easy or hard was it for you to swallow one of the pills?"



Acceptability of tablet.

9. Statistical Considerations

9.1. Statistical Hypotheses

This study will test the primary hypothesis that lasmiditan 200 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients at least 6 to less than 18 years of age. Additional hypotheses are described in Section 3.

9.2. Sample Size Determination

The study will have met its primary objective if lasmiditan 200 mg shows a statistically significant higher proportion of patients that are pain free at 2 hours after dosing relative to placebo. With a sample size of CCI pediatric patients in the primary efficacy analysis, the lasmiditan 200 mg group has CCI% overall power to be statistically significant compared with placebo in the proportion of patients that are pain free at 2 hours. The lasmiditan 50 mg and 100 mg groups have CCI% and CCI% overall power, respectively, to be statistically significant relative to placebo in the proportion of patients that are pain free at 2 hours. The study-wise 1-sided type I error rate is controlled at a 0.025 level.

To obtain these power values, it is assumed that the proportions of pediatric patients who are pain free at 2 hours after dosing will be CCI CCI CCI and CCI in the placebo, lasmiditan 50 mg, 100 mg, and 200 mg arms, respectively. These assumptions are based on results found in Derosier et al. (2012), Ho et al. (2012), and Winner et al. (2016) studies as well as results from adult pivotal trials in lasmiditan.

A hierarchical multiple testing procedure controls for multiplicity in testing the lasmiditan 200 mg, 100 mg, and 50 mg groups relative to placebo. Simulations were conducted to determine the power for each lasmiditan group relative to placebo using R Version 3.6.0. Additional simulation details as well as details of the testing scheme are provided in the statistical analysis plan (SAP).

It is assumed that approximately CCI% of enrolled patients will be eligible for randomization in Stage 2 and that CCI% of enrolled patients will be included for efficacy assessment. This is based on the average disposition in prior pediatric acute migraine trials with a placebo run-in enrichment design (Derosier et al. 2012; Ho et al. 2012; Winner et al. 2016). Based on these assumptions, the study will enroll approximately CCI patients to achieve the desired sample size of CCI children and adolescents in the efficacy analysis population.

9.3. Populations for Analyses

For purposes of analysis, the analysis populations are defined in the table below. Patient disposition in analysis populations is illustrated in Figure LAHV.1.

Table LAHV.5. Analysis Populations

Population	Description
All Randomized	All patients randomized to study medication at Visit 2.
Safety	All randomized patients who treat with at least 1 dose of study medication. CCI
Efficacy Analysis	CCI (placebo, LTN 50 mg, LTN 100 mg, or LTN 200 mg) in Stage 2. Patients will be included in the treatment group to which they are randomized in Stage 2.

Abbreviation: LTN = lasmiditan.

Figure LAHV.1. Analysis populations.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

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

Unless otherwise specified, efficacy analyses will be conducted for the efficacy analysis population and safety analyses will be conducted on the safety population.

Unless otherwise specified, analyses will be conducted for all pediatric patients and in the subgroups of patients at least 6 to less than [redacted] years of age and patients [redacted] to less than 18 years of age.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all efficacy and safety analyses unless otherwise stated. The 95% confidence intervals for all treatment group comparison estimates will be presented.

Treatment group comparisons for analyses relating to AEs will be assessed using exact Cochran-Mantel-Haenszel tests stratified by [redacted] across all patients and Fisher's exact tests within each age group. The age groups are

- at least 6 to less than [redacted] years of age, and
- [redacted] to less than 18 years of age.

For continuous data, descriptive statistics will be presented, including the mean, standard deviation, median, minimum, maximum, and sample size. For categorical data, sample size, frequency counts, and percentages will be presented.

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 or SAP. Additional exploratory analyses of the data will be conducted as deemed appropriate.

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.

9.4.1.1. Missing Data

The methodology for the primary efficacy analysis utilizes logistic mixed-effects regression modeling, where observed data at all time points up to 2 hours after dosing will be used to simultaneously estimate treatment effects for each lasmiditan group (50 mg, 100 mg, and 200 mg) at the 2-hour time point. A similar approach will be used for other efficacy analyses.

Patients who take additional medication for rescue will be classified as [redacted] in the efficacy analyses. For patients who are asleep at any given time point after dosing in Stage 2, all pain-related outcomes will be assumed to have achieved pain relief but not assumed to have achieved pain freedom. This modeling approach, which uses pseudo-likelihood-based estimation, has been shown to yield unbiased estimates when data are missing at random, regardless of the degree of missingness in the data (Little and Rubin 2002).

Please refer to the SAP for further details.

9.4.1.2. Patient Disposition

The number and percentage of patients who are screened, randomized, treated with study drug, and complete the End-of-Study Visit will be summarized.

9.4.1.3. Patient Characteristics

Patient characteristics will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups for the efficacy analysis Population and the safety Population. Treatment groups will be compared by using analysis of covariance techniques for continuous data and Pearson's chi-square or Fisher's exact test for categorical data.

Patient characteristics may include, but are not limited to

- demographics such as
  - age
  - sex
  - race
  - ethnicity
  - height
  - weight
  - body mass index, and
  - geographic region
- migraine history
- pubertal status
- menstrual status, and
- disability (PedMIDAS).

9.4.1.4. Concomitant Therapy

The number and percentage of concomitant medication use will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups for the safety analysis population. The number and percentage of patients who record use of additional medications for rescue medication use will also be summarized in the same manner.

9.4.1.5. Treatment Compliance

Treatment compliance data will be listed for the safety population.

9.4.2. Efficacy Analyses

All efficacy analyses will be performed on the efficacy analysis population.

9.4.2.1. Primary Analyses

The primary efficacy end point is the proportion of patients that are pain free at 2 hours after dosing, and the primary analyses will evaluate the efficacy of lasmiditan compared with placebo. The study will be declared to have met its primary objective if lasmiditan 200 mg shows a statistically significant higher proportion of patients that are pain free at 2 hours after dosing relative to placebo.

The primary analysis will be performed using a logistic mixed-effects regression model as a pseudo-likelihood-based mixed-effects repeated measures analysis. The analysis will include the fixed categorical effects of treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg), time point CCI [redacted] hours after dosing), and treatment-by-time point interaction as well as the fixed categorical covariates of CCI [redacted]. The age groups are

- at least 6 to less than CCI [redacted] years of age, and
- CCI [redacted] to less than 18 years of age.

An unstructured covariance structure for the random patient effect will be used to model within-patient correlation. The Kenward-Roger approximation (Kenward and Roger 2009) will be used to estimate denominator degrees of freedom. If the model does not converge under the default fitting algorithm, the Fisher's scoring algorithm will be implemented. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

1. Heterogeneous toeplitz
2. Heterogeneous first-order autoregressive
3. Toeplitz
4. First-order autoregressive.

Due to its robustness to covariance model choice, the sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters when the unstructured covariance matrix is not utilized. If the sandwich estimator is utilized, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions.

A hierarchical multiple comparisons procedure which tests lasmiditan 200 mg first, followed by lasmiditan 100 mg, and then lasmiditan 50 mg will be used to control type I error in the primary end point analysis.

Further details on the primary efficacy analysis, including sensitivity analyses, will be provided in the SAP.

9.4.2.2. Secondary Analyses

Logistic modeling will be used to analyze all secondary endpoints, with the exception of time to use of additional medication for rescue. Time to use of additional medication for rescue will be assessed using a Kaplan-Meier analysis and a log-rank test stratified by CCI [redacted].

Further details on the secondary efficacy analyses are provided in the SAP.

9.4.3. Analysis of Acceptability of Tablet

The proportion of patients with an acceptability rating of "very easy," "easy," "neither easy nor hard," "hard," or "very hard" at 24 hours after dosing will be summarized for the efficacy analysis population.

Further details are provided in the "Analysis of Acceptability of Tablet" section of the SAP.

9.4.4. Safety Analyses

TEAEs are defined as reported AEs that first occurred or ongoing events that worsen in severity within 48 hours after dosing with study medication. For patients who receive placebo in Stage 1 and lasmiditan in Stage 2, AEs that first occurred or worsened in severity while on placebo in Stage 1 will not be considered treatment emergent. 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 percentage of patients who experienced at least 1 TEAE will be summarized using Medical Dictionary for Regulatory Activities preferred terms nested within each system organ class by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups. TEAEs by maximum severity will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups. All AEs, SAEs, and AEs that lead to discontinuation of study medication will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups.

9.4.4.1. Vital Signs and Other Physical Findings

Vital signs will be collected at Screening and at Study Follow-Up and are not temporally related to lasmiditan dosing. As a result, interpretation of vital sign changes is limited.

Observed values for vital signs, height, weight, and body mass index will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups at Screening and at End-of-Study.

CCI [redacted]

9.4.4.3. Laboratory Tests

Laboratory parameters will be collected at Screening and at Study Follow-Up and are not temporally related to lasmiditan dosing. As a result, interpretation of laboratory parameter changes is limited. Age-appropriate normal laboratory values and clinical measurements will be used. Laboratory parameters will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups at Screening and at End-of-Study.

In addition, the number and percentage of patients with high or low results based on age-appropriate reference ranges at Screening and at End-of-Study will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups for each parameter.

A low result is defined as a change from a value greater than or equal to the low limit at screening to a value less than the low limit at End-of-Study. A high result is defined as a change from a value less than or equal to the high limit at screening to a value greater than the high limit at End-of-Study.

9.4.4.4. Cognition

The number and percentage of patients who report AEs and TEAEs that represent possible effects on cognition will be summarized by treatment group (placebo and All lasmiditan) and by lasmiditan dose groups using Medical Dictionary for Regulatory Activities preferred terms nested within system organ class. Additional details can be found in the SAP.

9.4.4.5. 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 (placebo and All lasmiditan) and by lasmiditan dose groups. In addition, the number and percentage of patients who experienced at least 1 of various composite measures will be presented and compared. 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
  - wish to be dead
- suicidal ideation or behavior.

9.4.5. Other Analyses

9.4.5.1. Subgroup Analyses

In addition to subgroup analyses by age groups, as previously described, other subgroup analyses will be performed for the primary efficacy end point. Table LAHV.6 provides definitions for each subgroup variable. The purpose of these analyses is to assess the consistency of treatment effects across the different subgroups.

Table LAHV.6. Definition of Subgroup Variables

Subgroup Variable	Categories
Use of preventive medication for migraine	Yes, no
Sex	Male, female
Racial origin (combine those with less than 10%)	American Indian/Alaskan Native Asian Black/African American Native Hawaiian/Pacific Islander White Multiple
Ethnicity	Hispanic or Latino, Not Hispanic or Latino
Region	European Union, North America (United States and Canada), Other

9.4.6. Data Monitoring Committee

A data monitoring committee (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. DMC membership will include, at a minimum, specialists with expertise in pediatrics, statistics, and other appropriate specialties.

The DMC will be authorized to review unblinded safety results by treatment group from interim analyses prior to database lock. The DMC may recommend as the following:

- stop study for safety
- modify study for safety, or
- continue with no modifications to the study.

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. Moreover, the study will not be stopped for positive efficacy results nor will it be stopped for futility; hence, no alpha will be spent. Details of the DMC, including its operating characteristics, will be documented in a DMC charter.

9.5. Interim Analyses

Interim analyses for safety are planned for this trial and will be reviewed by an independent DMC. The study will not be stopped for positive efficacy results nor will it be stopped for futility; hence, no alpha will be spent. Details of these interim analyses will be specified in the DMC charter and the interim analysis plan. Unblinding details are specified in a separate unblinding plan document.

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 ICH GCP Guidelines, and
- applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an Investigational Review Board (IRB) or Independent Ethics Committee (IEC) by the investigator and reviewed and approved by the IRB or IEC before the study is initiated.

Any amendments to the protocol will require IRB or 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

- providing written summaries of the status of the study to the IRB or IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB or IEC
- notifying the IRB or IEC of SAEs or other significant safety findings as required by IRB or IEC procedures
- providing oversight of the conduct of the study at the site and adherence to requirements of
  - 21 CFR
  - ICH guidelines
  - the IRB or 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 or her representative will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their parent or legal guardian will be required to provide a statement of informed consent or assent that meets the requirements of

- 21 CFR 50
- local regulations
- ICH guidelines
- Health Insurance Portability and Accountability Act requirements, where applicable, and
- the IRB or IEC or study center.

The medical record must include a statement that the parent or legal guardian consent and the participant assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent was obtained. The medical record should also describe how the clinical investigator determined that the person signing the ICF was the participant's legally authorized representative (parent or guardian). The authorized person obtaining the informed consent must also sign the ICF.

Participants and their parent or guardian must be reconsented and reassented to the most current version of the ICF(s) during their participation in the study.

If minor participants reach the age of legal consent during the course of the study, they must provide adequate informed consent in order to continue participating.

A copy of the ICF(s) must be provided to the participant or the participant's parent or legal guardian and be kept on file.

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.

10.1.5. 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, SAP, clinical study report (CSR), 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

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on a printed CRF or eCRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). 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. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must provide direct access to source data documents and permit

- study-related monitoring
- audits
- IRB or IEC review, and
- regulatory agency inspections.

The sponsor is responsible for granting electronic access to an eCRF and electronic Clinical Outcome Assessment (eCOA).

Monitoring details describing strategy (for example, 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 (central, remote, or on-site monitoring) 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 (for example, 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 1 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.

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 (participant-focused outcome instrument) will be collected by the participant, parent, or guardian via CCI and will be transcribed by the investigator site personnel into the EDC system.

Additionally, eCOA data (participant-focused outcome instrument) will be directly recorded by the participant, parent, or guardian CCI . 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 sponsor will be encoded and stored in the global product complaint management system.

10.1.7. Study and Site Closure

10.1.7.1. 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.

10.1.7.2. Discontinuation of Study Sites

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

10.1.8. 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 below will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 4 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Clinical laboratory collection can be done in nonfasting conditions.

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	Blood urea nitrogen (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 (females of childbearing potential)[a]
Ketones	Urine pregnancy test (local) (females of childbearing potential)
Bilirubin	Urine drug screen (patients aged ≥10 years)[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; RBC = red blood cell; WBC = white blood cell.

[a] Assayed by sponsor-designated central 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: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, CCI radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy, appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
    - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations:
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or

surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

- deficiencies in labeling information, and
- use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the Investigator's Brochure (IB) for lasmiditan in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very

important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the SAE coordinator by telephone.

Contacts for SAE reporting can be found in site training documents.

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the SAE coordinator.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in site training documents.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. 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, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements

10.4. Appendix 4: 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-LAHV Sampling Summary

Purpose	Planned[a] Blood Volume per Sample (mL)	Maximum[b] Number Samples	Planned[b] Total Amount (mL)
Screening tests[b]	4.0	3	12.0
Standard laboratory tests[b]	2.5	2	5.0
Total			17.0
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-designated Medical Monitor.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments

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	**Anti-nuclear antibody**[a]
AST	
GGT	**ALP Isoenzymes**[a]
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; 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 laboratory.

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

10.6. Appendix 6: Abbreviations and Definitions

Term	Definition
5-HT	5-hydroxytryptamine (serotonin)
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.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the 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
CK	creatine kinase
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, GCP, and applicable regulatory requirements.
CRF	case report form
C-SSRS	columbia-suicide severity rating scale
CT scan	computed tomography scan
DMC	data monitoring committee
CCI	[redacted]
[redacted]	[redacted]
eCRF	electronic case report form
eCOA	electronic Clinical Outcome Assessment

Term	Definition
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 ICF directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	US Food and Drug Administration
GCP	good clinical practice
GGT	gamma-glutamyl transferase
ICF	informed consent form
ICH	international council for harmonization
ICHD-3	international classification of headache disorders, 3rd edition
IEC	independent ethics committee
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 ICF.
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
MBS	most bothersome symptom
MRI	magnetic resonance imaging
PedMIDAS	pediatric migraine disability assessment scale
PGIC	patient global impression of change
PK	pharmacokinetic
PR	pulse rate

Term	Definition
PT-INR	prothrombin time-international normalized ratio
SAE	serious adverse event
SAC	statistical analysis center
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SUSARs	suspected unexpected serious adverse reactions 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
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.
t_{max}	time of peak plasma concentration
ULN	upper limit of normal

10.7. Appendix 7: EU-Country-Specific Requirements

The country-specific addenda reflected in this appendix must be performed in each of the respective countries, in addition to all procedures required by current version of Protocol H8H-MC-LAHV where applicable. The consolidation of these country-specific addenda into this appendix is to facilitate transition of this trial to the clinical trials information system under the new clinical trial regulation in Europe.

In this appendix, additions are designated using underline and deletions are designated using ~~strikethrough~~.

10.7.1. France-Specific Requirements

This country-specific appendix will apply to all investigational sites in France. This provides clarifications regarding exclusion criteria, concomitant therapy, end-of-study visit timing, and serious adverse event (SAE) reporting. In addition, the definition of the end of trial has been included.

Protocol Section 1.1 Synopsis

Summary of Study Design:

…

An End-of-Study Visit will be conducted within CCI days of dosing of study medication or after CCI weeks if no migraine attack is treated with study drug.

Intervention Groups and Duration:

…

Each patient's study participation will consist of

- a Screening Visit
- a Study Enrollment Visit
- a Treatment Period of up to CCI weeks in which the patient will be asked to treat a single qualifying migraine attack and complete outcome assessments, and
- an End-of-Study Visit within CCI days of treating a single migraine attack or after completion of Treatment Period without dosing.

Protocol Section 1.3 Schedule of Activities

	Screening*	Enrollment	Treatment Period	End-of-Study	ED	Notes
Visit	1	2	3**	801		
Target interval since previous visit	N/A	CCI				Site should schedule next visit for earliest possible date. Patients have up to CCI weeks to treat a single migraine attack as an outpatient. End-of-study visit to be scheduled after treatment of a single migraine attack or after completion of Treatment Period without dosing.

Protocol Section 4.1.4 End-of-Study Visit

An End-of-Study Visit will be conducted within CCI days of dosing of study medication or after CCI weeks if no attack is treated during the Treatment Period.

Protocol Section 4.4 End-of-Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study. A patient will be considered to have completed the study if they have completed Visit 1, Visit 2, Visit 3, and End-of-Study Visit. Patients may have completed the study without treatment of a qualifying migraine with study medication as long as they have completed the full CCI weeks of Visit 3 and End-of-Study Visit procedures.

Protocol Section 5.2 Exclusion Criteria

[10] Patient has a history or clinical evidence of congenital heart disease, suspected or confirmed, or clinical evidence of uncontrolled hypertension.

[29] Patient is ~~legally or~~ mentally incapacitated.

Protocol Section 6.5 Concomitant Therapy

Use of the following medications is prohibited for the duration of a patient's participation in the study from screening/Visit 1 through End-of-Study.

- any investigational treatment other than lasmiditan.

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 Adverse Events and Serious Adverse Events

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.

10.7.2. Germany-Specific Requirements

This country-specific appendix will apply to all investigational sites in Germany. This provides clarifications regarding concomitant therapy and discontinuation of inadvertently enrolled participants, according to regulatory agency feedback.

Protocol Section 6.5 Concomitant Therapy

Use of the following medications is prohibited, for the duration of a patient's participation in the study from Screening Visit 1 through End-of-Study:

- any investigational treatment other than lasmiditan.

Caution is required in case of coadministration 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.

Protocol Section 7.2.1 Discontinuation of Inadvertently Enrolled Patients

~~If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor clinical research scientist or clinical research physician agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the inadvertently enrolled participant to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.~~

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment and safety follow-up should be performed as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

10.8. Appendix 8. Protocol Amendment History

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

Amendment [a]: (09-Mar-2020)

Overall Rationale for the Amendment

Protocol H8H-MC-LAHV (Pediatric Options for Migraine Relief: A Randomized, Double-Blind, Placebo-Controlled Study of Lasmiditan for Acute Treatment of Migraine: PIONEER-PEDS1) 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 as needed to incorporate specific information on dosing for CCI [redacted], which was unavailable at time of initial protocol approval; updated dose justification section accordingly.
- Added stratification by use CCI [redacted] for migraine to statistical model for efficacy analysis based on regulatory input.
- Specified that patients who take additional medication for rescue will be classified as CCI [redacted] in the efficacy analyses based on regulatory input.
- Deleted pharmacogenetic sampling from trial.
- Made minor modifications to study schema, schedule of activities, and other tables and table footnotes for clarity.
- In addition, minor grammatical or typographical errors were corrected.

Section # and Name	Description of Change	Brief Rationale
Section 1, Synopsis, Intervention Groups and Duration subsection	Deleted sentence referring to future establishment of dose for CCI based on Study LAHX.	No longer relevant now that dosing has been established and is described elsewhere in protocol
Section 1, Synopsis, Statistical Analysis subsection	Added stratification by use of CCI to statistical model for efficacy analysis.	Regulator input
Section 1.2, Schema	Minor adjustments to figure and footnotes.	Clarified original intent
Section 1.3, Schedule of Activities	Deleted row referring to pharmacogenetic sampling and removed DNA from abbreviations footnote	Removed to reduce potential barrier to enrollment and to minimize blood volumes based on recommendations for restriction of total blood volumes in pediatric research
Section 2.2, Background	Changed reference In This Issue of Jama with Sun et al. 2013.	Clarified original content
Section 4.2, Scientific Rationale for Study Design, Additional Migraine Therapy subsection	Updated sentence regarding patients who take rescue medication before the 2-hour outcome assessment, to indicate that they will be classified as CCI in the efficacy analyses instead of being excluded from the efficacy population.	Regulatory input
Section 4.3, Justification for Dose	Deleted sentence referring to future establishment of dose for CCI patients based on Study LAHX. Also added a sentence.	No longer relevant now that dosing has been established and is described elsewhere in protocol
Section 4.3.1, Efficacy and Safety Data	Made minor clarifications (and swapped sequence of Sections 4.3.1 and 4.3.2).	Improved readability
Section 4.3.2, Pharmacokinetics	Replaced text about lasmiditan PK in adults with text about lasmiditan PK in children and adolescents, to explain how PK justifies using a weight cut-off to establish pediatric doses comparable to adult doses of 50 mg, 100 mg, and 200 mg for this study.	Supported establishment of dose as described elsewhere in protocol
Section 5.2, Exclusion criteria	Specified type of exclusion for patients with history of migraines.	Improved readability
Study 6.1, Study Intervention Administered	Updated dosing description to provide details about doses for patients in CCI	Provided details on dosing for CCI patients that were previously absent

Section 6.3, Measures to Minimize Bias: Randomization and Blinding	Added stratification by use of CCI [redacted] to description of Stage 2 randomization.	Regulatory input
CCI [redacted]	Made minor edits to table and footnotes for clarity.	Clarified original intent
Section 8.1.3.1, Other Pain-Related Outcomes	Clarified reference Tfelt-Hansen	Clarified original intent
Section 8.2.10, Puberty and Menstrual Status	Added sentence to clarify Pubertal status	Clarified original intent
Section 8.7, Genetics	Removed Section 8.7.1 requiring collection of whole blood sample for pharmacogenetic research and Section 8.7 text added	Removed to reduce potential barrier to enrollment and to minimize blood volumes based on recommendations for restriction of total blood volumes in pediatric research
Section 9.3, Populations for Analysis	Made minor edits to figure footnotes for clarity.	Clarified original intent
Section 9.4.1, General Statistical Considerations	Added stratification by use of CCI [redacted] to description of model to be used for treatment group comparisons of adverse events.	Regulatory input
Section 9.4.1.1, Missing Data	Updated information about patients who take rescue medication before the 2-hour outcome assessment, to indicate that they will be classified as CCI [redacted] in the efficacy analyses instead of being censored.	Regulatory input
Section 9.4.2.1, Primary Analyses	Added use of CCI [redacted] to description of model to be used for primary analysis.	Regulatory input
Section 9.4.2.2, Secondary Analyses	Added use of CCI [redacted] to description of model to be used for analysis of time to use of additional medication for rescue.	Regulatory input
Section 9.4.3, Analysis of Acceptability of Tablet	Made minor clarifications, changed wording	Improved readability
Section 9.4.5.1, Subgroup Analyses	Added use of CCI [redacted] to list of variables to be assessed in subgroup analyses of primary endpoint.	Regulatory input
Section 9.4.6, Data Monitoring Committee	Made minor clarifications, changed wording	Improved readability

Appendix 2	Clarified that pregnancy test (serum and urine) are administered to females of childbearing potential only. Deleted from table: Stored Samples Pharmacogenetic sample	Consistency with SOA
Appendix 3	Updated sampling volumes	Updated to accommodate removal of pharmacogenetic sampling
Section 11, References	Changed 1 reference and deleted 1 reference	Clarified original intent

Amendment [b]: (22-Jun-2023)

This amendment is considered to be substantial because, due to interim analysis outcome, it may have a significant impact on the number of participants.

Overall Rationale for the Amendment:

Protocol H8H-MC-LAHV(b) includes an interim futility analysis on the primary efficacy endpoint as an addition to Study LAHV and incorporate EU Clinical Trial Regulation (EU CTR) requirements into the main protocol.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Regulatory agency identifier numbers were added. New paragraph on study population was added. New paragraph on ethical consideration of benefit/risk was added	For harmonization of the protocol to meet EU CTR requirements
	Added a statement on interim futility analysis under statistical analysis	Due to addition of a futility analysis to the study
1.3. Schedule of Activities	Target interval since previous visit was updated as CCI days instead of CCI days under enrollment	For consistency
6.1. Study Intervention Administered	Added a table to list the interventions used	For harmonization of the protocol to meet EU CTR requirements
	Added a paragraph on packaging and labeling	
8.2.5.1. Hepatic Safety Monitoring	Revised section to provide more detailed guidance regarding monitoring requirements in the event of a qualifying event	For consistency with FDA liver safety guidelines
9.4.1. General Statistical Consideration	Added a sentence on handling of missing, unused, and spurious data	For harmonization of the protocol to meet EU CTR requirements
9.4.6. Data Monitoring Committee	Section 9.4.6 describes the process of the interim futility analysis conduct such that the study team remains blinded to the futility analysis results. The roles of the SAC and DMC are delineated	To add review of interim futility analysis results to the responsibilities of the DMC
9.5. Interim Analyses	The sentences "The study will not be stopped for positive efficacy results nor will it be stopped for futility. Hence no alpha is spent" were removed	Due to addition of a futility analysis to the study
9.5.1. Futility Analysis	Section 9.5.1 explains the addition of an interim futility analysis to the study as well as the rationale behind the	To summarize the interim futility analysis rationale and criteria

Section # and Name	Description of Change	Brief Rationale
	selection and interpretation of the futility analysis criteria	
10.1.1. Regulatory and Ethical Considerations	Additional statement highlighting the responsibility of the investigator was added	For harmonization of the protocol to meet EU CTR requirements
10.1.4. Data Protection	Revised section to provide more information on data protection	
10.1.5. Dissemination of Clinical Study Data	Revised section to provide more guidance on dissemination of clinical study data	
10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting	Added a new appendix on AE, SAE, definitions, and procedures for recording, evaluating, follow-up, and reporting	
10.6. Appendix 6 – Abbreviations and Definitions	Added abbreviation and its definition	For consistency
10.7. Appendix 7: EU-Country-Specific Requirements	Added a new appendix applicable to EU only sites by including the content from protocol addenda	For harmonization of the protocol and to avoid country-specific protocol versions in the EU to meet EU CTR requirements
11. References	Added one reference	The reference has been used in this document
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

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Approval	PPD Medical Director 16-Jan-2024 15:59:44 GMT+0000

Approval	PPD Statistician 16-Jan-2024 16:25:11 GMT+0000

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