Protocol: H8H-MC-LAHX

A Phase 1, Open-Label, Single-Dose Pharmacokinetic Study of Lasmiditan in Pediatric Patients with Migraine

NCT03988088

Approval Date: 29-Mar-2019

A Phase 1, Open-Label, Single-Dose Pharmacokinetic Study of Lasmiditan in Pediatric Patients with Migraine

Lasmiditan (LY573144)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 29-Mar-2019 GMT

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1. Protocol Summary

1.1. Protocol Synopsis

Title of Study:

A Phase 1, Open-Label, Single-Dose Pharmacokinetic Study of Lasmiditan in Pediatric Patients with Migraine.

Rationale:

This study is being conducted to determine the pharmacokinetics (PK), safety, and tolerability of lasmiditan in pediatric patients with migraine following a single oral dose.

Objectives/Endpoints:

Objectives	Endpoints
Primary To assess the single-dose pharmacokinetics of lasmiditan in pediatric migraine patients	Pharmacokinetic parameters including: • Maximum observed drug concentration (C_{max}) • Time to reach C_{max} (t_{max}) • Area under the concentration-versus-time curve (AUC) from time zero to infinity ($AUC_{[0-\infty]}$) • AUC from time zero to the time t, where t is the last time point with measurable concentration ($AUC_{[0-tlast]}$)
Secondary To assess the safety and tolerability of a single dose of lasmiditan in pediatric migraine patients	Summary of: • SAEs • AEs • ECG • vital signs
Exploratory To assess the safety, tolerability, and pharmacokinetics of lasmiditan in Japanese pediatric migraine patients	Pharmacokinetic parameters including: • C_{max} • t_{max} • $AUC_{[0-\infty]}$ • $AUC_{[0-tlast]}$ Summary of adverse events, SAEs, ECG, and vital signs.

Abbreviations: AE = adverse event; ECG = electrocardiogram; SAE = serious adverse event.

Summary of Study Design

This is a Phase 1, multicenter, open-label, single-dose study to determine the PK, safety, and tolerability of lasmiditan in pediatric patients with a diagnosis of migraine.

Treatment Arms and Planned Duration

Two cohorts will be evaluated concurrently:

- Primary **Cohort 1**: 15 kg to ≤40 kg
- Secondary **Cohort 2**: >40 kg to ≤55 kg

The planned doses for Cohorts 1 and 2 are 100 mg and 200 mg, respectively.

Visit 1: Screening

All patients are screened to determine if they are eligible to participate in the study.

Screening will occur up to 28 days to 3 days prior to lasmiditan dosing.

Visits 2–3: Dosing and PK Assessments

Day 1 (Visit 2)

- Patients arrive at the Clinical Research Unit (CRU) for assessments prior to dosing.
- Patients receive the single lasmiditan dose.
- Patients can go home after the 12-hour assessments. Patients may be offered the opportunity to spend the night depending on CRU capabilities.

Day 2 (Visit 3)

- Patient assessments are done at the CRU approximately 24 hours after dosing.

Visit 4/801

Visit 4/801 will occur approximately 14 days after dosing.

Visit 801 – Patients in Japan and those who will not proceed to the 3-month addendum will complete assessments according to Visit 801 in the Schedule of Activities.

Visit 4 – Patients continuing to the addendum will complete assessments according to the Schedule of Activities in the addendum.

Number of Patients
Cohort 1
Approximately 13 patients may be enrolled to obtain 11 patients with evaluable PK data.

Cohort 2
Approximately 8 patients may be enrolled to obtain 6 patients with evaluable PK data.

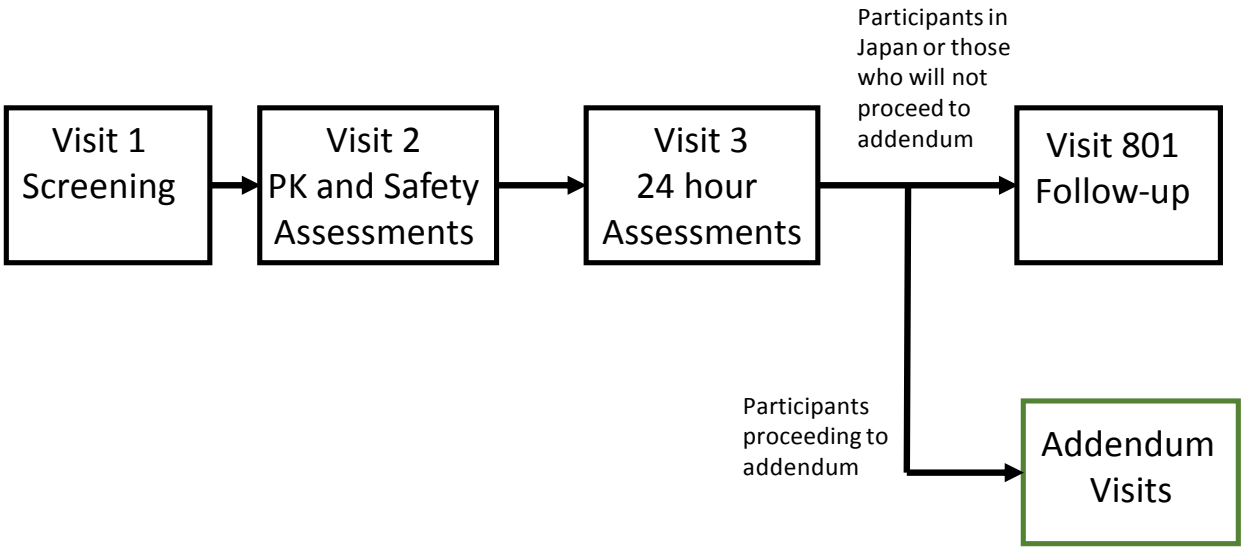
Statistical Analysis:

Safety parameters that will be assessed include:

- adverse events including clinically significant electrocardiograms
- serious adverse events
- vital signs
- Columbia-Suicide Severity Rating Scale (C-SSRS) assessments
- Cognition, as assessed by Cogstate Pediatric Brief Battery

Pharmacokinetic parameter estimates for lasmiditan will be calculated by standard noncompartmental methods of analysis from plasma lasmiditan concentrations, and listed and summarized using descriptive statistics.

1.2. Schema



Abbreviation: PK = pharmacokinetic.

1.3. Schedule of Activities

Table LAHX.1. Schedule of Activities for Patients Participating in the Open-Label PK Study

Study Period (SP)	SP I Screening	SP II PK Assessment/Safety											ED[a]	SP III	Notes
Visit	1	2										3		4/801[b]	
Time from Lasmiditan Dose (hr)		Predose	Dose	0.5	1	1.5	2	3	4	8	12	24			
Study Day	-28 to -3	Day 1										Day 2		Day 14±3	
Assessments and Procedures															
Informed consent/Assent	X														
Inclusion/exclusion criteria review	X	X													
Demographics	X														
Medical history	X	X													
Substance use history	X	X													Alcohol and tobacco use for patients aged ≥10 years
Concomitant medications	X	X	X									X	X	X	At screening, previous and ongoing migraine treatments will be collected.
Physical examination	X											X	X	X	
Targeted neurologic examination		X					X			X		X			
Height	X														Height will be measured using a stadiometer and measured in triplicate.
Weight	X	X												X	Weight will be measured once.
Menstrual status	X														
12-lead ECG (single)	X	X										X			ECG procedure occurs prior to blood draws and dosing. Patients must be supine for at least 5 minutes before collection and remain supine but awake during the

Study Period (SP)	**SP I Screening**	**SP II PK Assessment/Safety**											**ED[a]**	**SP III**	**Notes**
Visit	**1**	**2**										**3**		**4/801[b]**	
Time from Lasmiditan Dose (hr)		**Predose**	**Dose**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**			
Study Day	**-28 to -3**	**Day 1**										**Day 2**		**Day 14±3**	
															procedure.
Vital signs Blood pressure and pulse	X	X			X		X		X		X	X	X	X	At screening – single measurement. All other time points – triplicate measurements, and prior to blood draws and lasmiditan administration. Blood pressure measurements will be taken by an automated calibrated (if calibration is required) machine.
Orthostatic Vital Signs	X	X			X		X					X			
Temperature	X	X													
Adverse events		X	X									X	X	X	
Lasmiditan dosing			X												
Clinical Laboratory Tests and Sampling															
Hematology	X	X										X			
Clinical chemistry	X	X										X			
Gonadal hormones	X														Estradiol (for females) or testosterone (for males) will be collected in patients aged 8 to <18 years, to assess pubertal status.
Urinalysis	X														
Urine drug screen	X	X													For patients aged ≥ 10 years.

Study Period (SP)	**SP I Screening**	**SP II PK Assessment/Safety**											**ED[a]**	**SP III**	**Notes**
Visit	**1**	**2**										**3**		**4/801[b]**	
Time from Lasmiditan Dose (hr)		**Predose**	**Dose**	**0.5**	**1**	**1.5**	**2**	**3**	**4**	**8**	**12**	**24**			
Study Day	**-28 to -3**	**Day 1**										**Day 2**		**Day 14±3**	
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. If a patient discontinues within 24 hours of the lasmiditan dose, an early discontinuation urine test is not needed.
PK blood sample				X	X	X	X	X	X	X	X	X			An indwelling catheter is required for blood collection on Day 1. See Notes for time windows and order of procedures.
Scales and Questionnaires															
C-SSRS Children's version SHSF, SHFU	X	X										X	X	X	Suicidal ideation and behavior subscales excerpt – Adapted for the assessment of 11 preferred ideation and behavior categories. The C-SSRS will be scored only in patients ≥7 years old. The Self-Harm Follow-Up Form is required only if triggered by the Self-Harm Supplement Form.
Cogstate Pediatric Brief Battery	X	X					X			X		X		X	Participants will be instructed on use at screening.

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; PK = pharmacokinetic; SHFU = Self-Harm Follow-Up form; SHSF = Self-Harm Supplement form.

[a] Early discontinuation procedures should be conducted if a patient discontinues from the study before follow-up visit.

[b] Visit 801 – For patients in Japan and those who will not proceed to the 3-month addendum. Visit 4 – Patients continuing to the addendum will complete assessments according to the Schedule of Activities in the addendum.

Note: If multiple procedures take place at the same time point, the following order of the procedure should be used:

ECG, vital signs and orthostatic vital signs, and venipuncture.

Where venipuncture and other procedures take place at the same time point, the following time windows for obtaining blood samples should be maintained:

>0 to 2 hours postdose: ±5 minutes

2.5 to 6 hours postdose: ±10 minutes

>6 to 12 hours postdose: ±20 minutes

12 hours postdose: ±30 minutes

24 hours postdose: ±60 minutes.

Where repeats of vital signs measurements are required, repeats should be performed after venipuncture.

2. Introduction

2.1. Study Rationale

This study is being conducted to determine the pharmacokinetics (PK), safety, and tolerability of lasmiditan in pediatric migraine patients following a single oral dose of lasmiditan.

This study is part of a pediatric (6 to 18 years) clinical program for lasmiditan. The data from this study will be used to inform dose selection in subsequent clinical studies intended to provide pivotal efficacy and safety data to support use of lasmiditan for acute treatment of migraine in children and adolescents.

This study will also include Japanese pediatric patients to facilitate lasmiditan pediatric clinical development in Japan.

2.2. Background

Lasmiditan is being developed as a novel therapy for the acute treatment of migraine. Lasmiditan is a high-affinity, centrally penetrant, selective human serotonin 1F (5-HT_{1F}) receptor agonist that exerts its therapeutic effects in the treatment of migraine by decreasing neuropeptide release and inhibiting pain pathways, including the trigeminal nerve. 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.

Across clinical trials in adults, lasmiditan was generally well tolerated and the majority of adverse events (AEs) were mild to moderate, with a duration of 1 to 5 hours for the common treatment-emergent adverse events (TEAEs). Lasmiditan use is associated with neurologic TEAEs, with the most common being dizziness, paresthesia, somnolence, fatigue, nausea, hypoesthesia, and muscle weakness. In a variety of analyses of Phase 3 data, proportions of adult patients reporting TEAEs generally decreased over time.

In the pivotal efficacy trials in adults, doses of 50 mg, 100 mg, and 200 mg were studied. All doses were superior to placebo in the primary and key secondary endpoints of pain freedom and freedom from most bothersome symptoms. A consistent dose–response relationship was observed, with patients in higher dose groups having a greater likelihood of response across multiple efficacy endpoints. Based on these data in adults with migraine, lasmiditan may provide therapeutic benefit to children and adolescents from 6 to <18 years of age with migraine.

A population pharmacokinetic (popPK) analysis of adult PK data following oral administration indicates that lasmiditan is rapidly absorbed with a median time to reach maximum observed drug concentration (t_{max}) of 1.8 hours and is eliminated with a geometric mean value of 5.7 hours for terminal half-life. Over the clinical dose range of 50 to 200 mg, lasmiditan exposure generally increases linearly with dose. The interindividual variability of lasmiditan maximum observed drug concentration (C_{max}) and area under the concentration-versus-time curve (AUC) are 43% and 39%, respectively, based on the popPK analysis. The covariates of body weight, age [elderly vs. nonelderly], and population [healthy vs. patient] were statistically significant in the

popPK model, but the magnitude of these effects was within the PK variability and therefore not considered to be clinically relevant over the range of covariate values in the population.

2.3. Benefit/Risk Assessment

This is an open-label study in which all pediatric patients will receive a single dose of lasmiditan. Participants in the United States (US) will have the opportunity to participate in an open-label, 3-month addendum to this study.

Participants will also have the opportunity to participate in an open-label, 12-month long-term safety study (Study H8H-MC-LAHW) when it is available.

As a centrally penetrant and neurally active drug, lasmiditan use is associated with neurologic 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 are mild to moderate and self-limiting.

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

3. Objectives and Endpoints

Table LAHX.2 shows the objectives and endpoints of the study.

Table LAHX.2. Objectives and Endpoints

Objectives	Endpoints
Primary To assess the single-dose pharmacokinetics of lasmiditan in pediatric migraine patients	Pharmacokinetic parameters including: • Maximum observed drug concentration (C_{max}) • Time to reach C_{max} (t_{max}) • Area under the concentration-versus-time curve (AUC) from time zero to infinity ($AUC_{[0-\infty]}$) • AUC from time zero to the time t, where t is the last time point with measurable concentration ($AUC_{[0-tlast]}$).
Secondary To assess the safety and tolerability of a single dose of lasmiditan in pediatric migraine patients	Summary of: • SAEs • AEs • ECG • vital signs
Exploratory To assess the safety, tolerability, and pharmacokinetics of lasmiditan in Japanese pediatric migraine patients	Pharmacokinetic parameters including: • C_{max} • t_{max} • $AUC_{[0-\infty]}$ • $AUC_{[0-tlast]}$ Summary of adverse events, SAEs, and vital signs.

Abbreviations: AE = adverse event; ECG = electrocardiogram; SAE = serious adverse event.

4. Study Design

4.1. Overall Design

This is a Phase 1, multicenter, open-label, single-dose study to determine the PK, safety, and tolerability of lasmiditan in pediatric patients with a diagnosis of migraine.

Two cohorts will be evaluated concurrently:

- Primary **Cohort 1**: 15 kg to ≤40 kg
- Secondary **Cohort 2**: >40 kg to ≤55 kg

The planned doses for Cohorts 1 and 2 are 100 mg and 200 mg, respectively.

Visit 1: Screening

All patients are screened to determine if they are eligible to participate in the study.

The study and potential risks are explained to the patient and their parent or guardian.

The informed consent form (ICF) and patient assent form must be signed before any study procedures are performed.

Screening will occur 28 days to 3 days prior to lasmiditan dosing.

Visits 2–3: Dosing and PK Assessments

Enrolled patients and patient's parent or guardian will receive instructions regarding study procedures prior to dosing.

Day 1 (Visit2)

- Patients arrive at the Clinical Research Unit (CRU) for assessments prior to dosing.
- Patients receive the single lasmiditan dose.
- Patients can go home after the 12-hour assessments. Patients may be offered the opportunity to spend the night depending on CRU capabilities.

Day 2 (Visit 3)

- Patient assessments are done at the CRU approximately 24 hours after dosing.

Visit 4/801

Visit 4/801 will occur approximately 14 days after dosing.

Visit 801 – Patients in Japan and those who will not proceed to the 3-month addendum will complete assessments according to Visit 801 in the Schedule of Activities.

Visit 4 – Patients continuing to the addendum will complete assessments according to the Schedule of Activities in the addendum.

4.2. Scientific Rationale for Study Design

This is an open-label, single-dose study to determine the PK, safety, and tolerability of lasmiditan in pediatric migraine patients. This study is part of a pediatric migraine clinical development program, and the data from this study will be used to inform dose selection in subsequent clinical studies intended to provide pivotal efficacy and safety data to support use of lasmiditan for acute treatment of migraine in children and adolescents.

The single-dose administration:

- limits exposure of patients to lasmiditan, compared with repeat dosing
- is consistent with the intended use of lasmiditan as a medication that is taken on an "as needed" basis for abortive treatment of migraines
- is appropriate to assess PK, safety, and tolerability of lasmiditan.

Body Weight Selection

The lower end of the weight range for this study is 15 kg, as only 1% of pediatric subjects who are 6 years of age weigh < 15 kg, based on US pediatric growth charts. Additionally, in Japan, <3% of pediatric subjects who are 6 years of age weigh < 15.6 kg (Kato et. al. 2014).

The higher end of the weight range for this study is 55 kg. The body weight evaluated in adults ranged from 48 to 115 kg, with limited exposure data in subjects ≤55 kg (lower 5th percentile). Therefore, the body weight range of 15 to 55 kg is considered suitable for evaluation in this study. For body weights above 55 kg, the pediatric exposure of lasmiditan is anticipated to be similar to that of adults of the same body weight for a given dose.

Pharmacokinetics

This study is designed to characterize the PK of lasmiditan after a single dose of lasmiditan. Blood samples will be collected for 24 hours after dosing, which is considered adequate to characterize the PK profile in pediatric patients. The plasma concentration of lasmiditan is an objective measurement; therefore, the open-label design is appropriate for this evaluation.

Japanese Patients

Data from Japanese pediatric patients will be used to inform subsequent clinical studies in Japanese patients.

4.3. Justification for Dose

The planned doses for this study are 100 mg for patients who are 15 to ≤40 kg and 200 mg for patients who are >40 to ≤55 kg.

Efficacy and Safety Data

Efficacy and safety data in adults support the use of 50 mg, 100 mg, and 200 mg of lasmiditan for the acute treatment of migraine. Although lower doses were statistically superior to placebo on pain freedom at 2 hours, the proportion of patients achieving pain freedom at 2 hours after a

migraine attack in adult Phase 3 studies was numerically highest for the 200-mg dose. It is important to assess pediatric dose(s) predicted to achieve exposures comparable to adult 200-mg exposure, because demonstrating efficacy in pediatric migraine studies has been challenging, in part because of the high placebo rates reported in these studies (Evers 2006; Fernandes 2008).

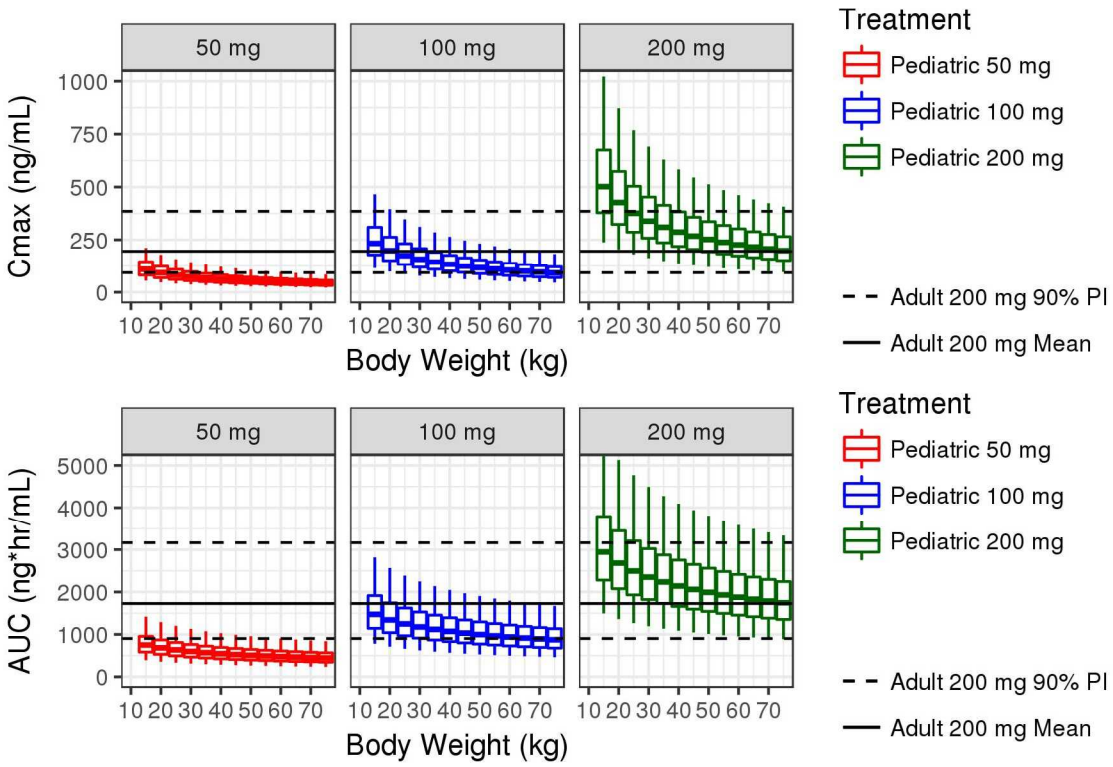
Although 200 mg was the highest dose tested in the Phase 3 migraine program, lasmiditan was generally well tolerated in adults, including Japanese adults, up to 400 mg in Phase 1 and 2 studies. Also, the margin of safety for the 200-mg dose is estimated to be approximately 3 times, based on the ratio of the observed no-observed-adverse-effect-level exposure from the juvenile toxicology study to the estimated human exposure at 200 mg.

Dose Levels and Weight Ranges

The planned dose levels and weight ranges are supported by model-based simulations of pediatric exposures. A popPK model was developed using PK data following oral dosing in adult patients pooled from multiple Phase 1 studies. In the model, the effect of body weight on apparent total body clearance and volume of distribution resulted in lower lasmiditan exposure in heavier patients relative to lighter patients. Model-based simulations were subsequently performed to predict lasmiditan exposures in pediatric patients at 5-kg body weight increments (Figure LAHX.1).

The maximum observed drug concentration (C_{max}) was considered the primary exposure measure used to guide dose selection, as it is expected to be a more relevant response for acute treatment. For pediatric patients (15 to ≤40 kg) receiving 100 mg, the predicted ratio of mean C_{max} ranged from 0.68 for 40 kg to 1.19 for 15 kg, relative to that of adults receiving 200 mg. For pediatric patients (>40 kg to ≤55 kg) receiving 200 mg, the predicted ratio of mean peak exposure C_{max} ranged from 1.22 for 55 kg to 1.37 for 45 kg, relative to that of adults receiving 200 mg.

Therefore, the proposed dosing regimen should provide exposures in pediatric patients, comparable to the predicted range of adult 200-mg exposures. PK exposure data will be reviewed during the study. The dose may be adjusted, if lasmiditan exposure is substantially different from PK predictions.



Abbreviations: AUC = area under the concentration-versus-time curve; C_{max} = maximum observed drug concentration; PI = prediction interval.
The boxes depict geometric mean and the interquartile range; whiskers depict 90% prediction interval (PI) in pediatric subjects. The black solid and dashed lines depict the geometric mean exposure value and 90% PI for 200 mg dose in adults, respectively.

Figure LAHX.1. Predicted lasmiditan C_{max} and AUC values for pediatric subjects.

4.4. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities for the last patient.

5. Study Population

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

5.1. Inclusion Criteria

Study investigator(s) will review patient history and screening test results at Visit 1 and Visit 2 to determine if the patient meets all inclusion and none of the exclusion criteria to qualify for enrollment in the study. All screening activities must be completed and reviewed before the patient is enrolled and receives the investigational product.

A patient is eligible for inclusion in the study only if all the criteria apply at screening.

Type of Patient and Disease Characteristics

[1] Patient is between 6 and <18 years of age.

[2] have a history of migraine with or without aura, as defined by International Headache Society International Classification of Headache Disorders, 3rd edition guidelines (ICHD-3 2018) migraine definitions and meets the following criteria:

- history of migraine attacks for more than 6 months
- reports ≥2 and ≤15 migraine attacks per month in the 2 months prior to screening

[3] are migraine free on day of lasmiditan administration at the time of predose assessments.

[4] have a minimum body weight of 15 kg and a maximum of 55 kg.

[5] are able to swallow a tablet.

[6] have received age-appropriate immunizations according to their country-specific public health policy as confirmed by patient's immunization record.

Informed Consent and Patient Agreements

[7] the patient and the 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.

[8] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[9] 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, such as Facebook, Twitter, Snapchat, Instagram, Google+, until notification that the study has completed.

[10] Are male or female

If female, must agree to abide by the following guidance:

- Adolescent females who have started menses (even 1 cycle and any amount of spotting) are considered to be of childbearing potential.
- Females of childbearing potential must agree to use a highly effective method of contraception (that is, one with less than 1% failure rate) such as combination oral contraceptives, implanted/injected contraceptives, intrauterine devices, or a 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, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Females not of childbearing potential may participate and include those who are infertile because of surgical sterilization by hysterectomy, bilateral oophorectomy, or tubal ligation, or who have a congenital anomaly such as mullerian agenesis.

5.2. Exclusion Criteria

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

Medical Conditions

[11] Have a history or clinical evidence of congenital heart disease, suspected or confirmed; or a history of stroke.

[12] Have electrocardiogram (ECG) showing abnormalities compatible with acute cardiovascular events and/or serious cardiovascular disease risk.

[13] Have had myocardial infarction, unstable angina, percutaneous coronary intervention, or coronary artery bypass graft within 6 months of screening.

[14] Have planned cardiovascular surgery or percutaneous coronary angioplasty.

[15] Have liver tests outside the normal range 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.

Exceptions

- if test results outside the normal range are discussed and judged not clinically significant by Eli Lilly and Company (Lilly) Medical
- Patients with TBL ≥1.5x ULN and the following criteria for Gilbert syndrome:
  - Bilirubin is predominantly indirect (unconjugated) at screening (direct bilirubin within normal limits)
  - Absence of liver disease
  - ALT, aspartate aminotransferase (AST), and ALP ≤1x ULN at screening
  - Hemoglobin not significantly decreased at screening.

[16] Have, 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.

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

[18] At baseline:

- have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS), or
- have 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.

[19] Are pregnant or nursing.

[20] Have, 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

[21] Have used opioids or barbiturate-containing analgesics >3x per month for the treatment of pain in more than 2 of the past 6 months (opioid administration in an emergency setting [either urgent or emergent] may be an exception.).

[22] Have a history of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or are currently using drugs of abuse (including opioids, barbiturates, and marijuana), or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence.

[23] Have a positive urine drug screen for any substances of abuse. One retest is allowed if the urine drug screen is positive, at the investigator's discretion.

[24] Are on a CNS active drug, which is known to affect levels of attention or sedation, such as a benzodiazepine for sleep or anxiety, or stimulants for Attention Deficit Hyperactivity Disorder.

[25] Have known allergies to lasmiditan, related compounds, or any components of the formulation.

Diagnostics Assessments

[26] Have a history of any type of headache except for migraine with or without aura, tension type headache or medication overuse headache, as defined by ICHD 3. Migraine subtypes including sporadic or familial hemiplegic migraine and migraine with brainstem aura, previously known as basilar type migraine, should be excluded.

[27] Have a history of traumatic head injury associated with significant change in the quality or frequency of their headaches, including a new onset of migraine following traumatic head injury or a history of post-traumatic headache.

[28] Have a known history of intracranial tumors or developmental malformations including Chiari malformations.

Prior/Concurrent Clinical Trial Experience

[29] Are 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.

[30] Have 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.

[31] Have previously completed or withdrawn from this study or any other study investigating lasmiditan, and have previously received the investigational product.

Other Exclusions

[32] Are legally incapacitated.

[33] Are children of investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, biological or guardian, child, or sibling.

[34] Are children of Lilly employees.

[35] Have donated more than a single unit of blood within 4 weeks prior to screening or intend to donate blood during the course of the study.

[36] In the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

5.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [11] through [20] exclude medical conditions, [21] through [28] exclude concomitant medication, substances of abuse, and medical history that may confound the assessment of study endpoints, [29] through [31] exclude concurrent clinical trial experience, and [33] and [34] prevent conflict of interest in study participants.

5.3. Lifestyle and/or Dietary Considerations

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

5.3.1. Meals and Dietary Restrictions

Patients will:

- fast overnight prior to the day of dosing with the exception of a light breakfast, such as cereal with fat-free milk or toast or white rice, 2 hours prior to the time of dosing
- abstain from water 1 hour before and after dosing, except for up to 240 mL of water given with the dose
- fast until approximately 2 hours after dosing, at which time a meal will be served.

5.3.2. Caffeine, Alcohol, and Tobacco

From approximately 48 hours prior to dosing, and up to 24 hours after dosing, patients are not allowed to:

- consume xanthine- or caffeine-containing food and drink
  Examples - cola, chocolate drinks, tea, coffee, and energy drinks containing methylxanthine (caffeine, theophylline, or theobromine)
- consume alcoholic beverages
- use tobacco products.

Limits may be adjusted to meet local requirements if local requirements are more stringent.

5.4. Screen Failures

At Visit 2, inclusion and exclusion criteria will be reviewed prior to the first dose of investigational product.

Screen failures are defined as patients who consent to participate in the study but do not meet the enrollment criteria and do not receive any dose of investigational product.

Based on the clinical judgment of the investigator, patients who fail to qualify at enrollment may be rescreened at a later date. Only 1 rescreening visit is permitted.

If rescreening is performed, the parent or guardian and the patient must sign a new assent and ICF, and the patient will be assigned a new identification number.

If changes in circumstances have allowed a patient to be rescreened, a complete screening visit must be repeated. However, if the rescreen visit is within 30 days from the original screening visit and it was a result of only specific out-of-range value/findings, then only those assessments should be repeated and not the entire laboratory panel.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. Treatment

6.1. Treatment Administered

Lasmiditan 50-mg and 100-mg tablets will be used in this study, to achieve a single total dose of either 100 mg or 200 mg (Table LAHX.3). The investigator will decide which tablet strength to administer to achieve the appropriate dose based on the patient's ability to swallow and patient's preference.

Lasmiditan will be administered orally, on Day 1, in a sitting position. The actual time of the dose administered will be recorded in the patient's case report form (CRF).

Patients should not lie supine for 2 hours after dosing, unless clinically indicated or for study procedures.

Table LAHX.3. Planned Treatment Regimen

Cohort	1	2
Patient Body Weight	15 kg to ≤ 40 kg	>40 kg to ≤ 55 kg
Treatment Name	Lasmiditan	Lasmiditan
Dosage Formulation	Tablet	Tablet
Unit Dose Strength(s)/ Dosage Level(s)	50 mg x2 or 100 mg x1	50 mg x4 or 100 mg x2
Route of Administration	Oral	Oral
Dosing Instructions	With approximately 240 mL of room temperature water in a sitting position	

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- and returning all unused medication to Lilly or its designee at the end of the study

6.1.1. Packaging and Labeling

Lasmiditan will be supplied to the clinics with bulk bottles of 50-mg and 100-mg tablets. The investigational product will be labeled according to the country's regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm all investigational product was received in good condition, and any discrepancies are reported and resolved before use of the study drug.

Only patients enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product should be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. Patients who meet all criteria for enrollment at Visit 2 will receive a dose of lasmiditan 100 mg or 200 mg, according to their body weight, as shown in Table LAHX.3.

6.4. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

6.5. Concomitant Therapy

For patients taking preventive medication for migraine, treatment regimen must be stable for at least 3 months prior to Visit 1.

This study will be conducted during a migraine-free period; therefore concomitant acute medications for migraine or migraine symptoms on the day of Visit 1 are not allowed, with the exception of acetaminophen, which may be administered at the discretion of the investigator, according to label recommendations.

A topical anesthetic cream may be used by the investigator to reduce discomfort associated with cannula/needle insertion.

If the need for concomitant medication other than acetaminophen or topical anesthetic arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with Lilly medical. All concomitant medications, whether prescription or over the counter, used at baseline and/or during the course of the study, must be recorded on the appropriate Concomitant Medication CRF.

6.6. Dose Modification

The planned dose is 100 mg and 200 mg in pediatric patients with body weight ≥15 kg to ≤40 kg and >40 kg to ≤55 kg, respectively. Safety and PK data will be reviewed on an ongoing basis.

Doses may be adjusted when data are available from at least 3 patients with evaluable PK data in the primary cohort (Section 9.4.3).

6.7. Treatment after the End of the Study

This section is not applicable to this study.

7. Discontinuation of Study Treatment and Participant Discontinuation and Withdrawal

7.1. Discontinuation from Study Treatment

This is a single-dose study. If a patient discontinues after receiving the single dose of lasmiditan, early discontinuation procedures will be completed per the Schedule of Activities of this protocol.

7.2. Participant Discontinuation and Withdrawal from the 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).
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study.
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.
- Patient Decision
    - the patient requests to be withdrawn from the study, or
    - the parent or patient's guardian requests that the patient be withdrawn 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.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between Lilly Medical and the investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from Lilly Medical to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

Safety follow-up is as outlined in Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of this protocol.

7.3. Patients Lost to Follow-Up

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

8. Study Assessments and Procedures

The Schedule of Activities details the study procedures and their timing (including tolerance limits for timing).

Appendix 2 lists the laboratory tests that will be performed for this study. A separate table in this section provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Unless otherwise stated in 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

This section is not applicable to this study.

8.2. Safety Assessments

The Lilly clinical pharmacologist or Clinical Research Physician (CRP)/scientist will monitor safety data throughout the course of the study.

8.2.1. Physical Examination

For each patient, a complete physical examination (excluding pelvic and rectal examinations) will be performed according to the Schedule of Activities. A complete physical examination may be repeated at the investigator's discretion at any time a patient presents with physical complaints. A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

8.2.2. Vital Signs

For each patient, vital sign measurements should be conducted according to the Schedule of Activities.

Vital signs will consist of 1 pulse rate, 1 temperature, and 3 blood pressure (BP) measurements. Three consecutive BP readings will be recorded at intervals of at least 1 minute. Where applicable, the last triplicate vital sign can be used as the supine/semi-recumbent vital sign for the calculation of orthostatic changes.
Blood pressure and pulse rate measurements:

- will be taken when the patient is in a supine position
- should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (for example, television, cell phones)
- will be collected using the appropriate size pediatric BP cuffs
- will be assessed with a completely automated device
    - Manual techniques will be used only if an automated device is not available.

When orthostatic measurements are required, patients should be supine for at least 5 minutes and stand for at least 2 minutes. If the patient feels unable to stand, supine vital signs only will be recorded. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Any clinically significant findings from vital sign measurements that result in a diagnosis should be reported to Lilly or its designee as an AE via electronic case report form (eCRF).

Any abnormal finding for vital signs at 24 hours postdose will need to be repeated at follow-up to check if it has returned to baseline.

8.2.3. Electrocardiograms

For each patient, a single12-lead digital ECG will be collected according to the Schedule of Activities. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Electrocardiograms must be recorded before collecting any blood samples.

Patients must be in supine position for at least 5 minutes before ECG collection and remain supine, but awake during ECG collection.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present for immediate patient management, should any clinically relevant findings be identified.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

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

Any abnormal finding for ECGs at 24 hours postdose will need to be repeated at follow-up to check if it has returned to baseline.

8.2.4. 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.

Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via CRF.

Investigators must document their review of each laboratory safety report.

8.2.4.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT ≥3x ULN, ALP ≥2x ULN, or elevated TBL ≥2x ULN, liver tests (Appendix 3) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the CRP/CRS. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

- elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2x ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests
- patient discontinued from treatment because of a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

8.2.5.1. C-SSRS

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

Suicidality will be assessed by the children's version of the C-SSRS (Posner et al. 2011). The C-SSRS scale includes suggested questions to solicit information needed to determine if a suicide-related thought or behavior occurred during the assessment period.

The Self-Harm Supplement should be completed every time the patient is assessed by C-SSRS. If there are positive findings on the Self-Harm Supplement, then the Lilly Self-Harm Follow-Up form will be used to collect additional information to allow for a more complete assessment of these behaviors.

The C-SSRS and a corresponding Self-Harm Supplement Form will be used for assessment of the patient according to the Schedule of Activities by appropriately trained site personnel.

Before using the C-SSRS, study site personnel will question the patient about any change in the preexisting condition(s) and the occurrence and nature of any AEs.

Nonserious AEs obtained through the questionnaire are recorded and analyzed separately.

Only SAEs and AEs leading to discontinuation elicited through the C-SSRS are to be recorded as AEs via the CRF. Serious adverse events must be reported to Lilly or its designee within 24 hours as SAEs.

8.2.5.2. Columbia-Suicide Severity Rating Scale – Child Version

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and/or behavior during the assessment period. A children's version of the C-SSRS will be completed for all patients. The scale includes suggested questions to solicit the type of information needed to determine if suicidal ideation and/or behavior occurred. The C-SSRS is administered by qualified site personnel. The tool was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events. 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 nonleading AE collection should occur prior to the collection of the C-SSRS. If a suicide-related event is discovered during the C-SSRS, but was not captured during the nonleading AE collection, sites should not change the AE form. If an event is serious or leads to discontinuation, this is an exception where the SAE and/or AE leading to discontinuation should be included on the AE form and the process for reporting SAEs should be followed.

8.2.5.3. Self-Harm and Follow-up Supplement Forms

The Self-Harm Supplement Form is an administrative form to denote the presence of any reported self-harm events and is used to trigger a 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.

As part of the C-SSRS, the Self-Harm Follow-Up form will be completed for each event if the patient reports 1 or more self-harm events.

8.2.6. Cognition

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. Height and Weight

Height and weight will be assessed according to the Schedule of Activities.

- Height will be measured using a stadiometer and measured in triplicate.
- Weight must be measured 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 taken without shoes and after the removal of any heavy personal items (that is, large jewelry, wallets, coats, etc.).

8.2.8. Puberty and Menstrual Status

Pubertal status, including menstrual history, will be determined by the investigator at the screening visit based on an interview with the patient and the patient's guardian, and results of blood hormone levels.

8.2.9. Targeted Neurological Examination

A targeted neurological examination will be performed at the visits and times specified in the Schedule of Activities.

Examination	Components	Considerations
General	Speech	Monitor for dysarthria or other speech changes during neurological examination and interactions
Motor	Upper and lower extremity strength Tone	Assess for motor weakness Assess for decrease or increase in tone
Cerebellar	Arms extended Finger–nose–finger Heel to shin (supine) Rapid alternating movement (pronation/supination of one hand on opposite palm)	Assess for tremor and coordination; ataxia of lower extremities; dysdiadochokinesia
Gait	Casual Toe Heel Tandem	Assess for strength and coordination
Reflexes	Biceps Brachioradialis Patellar Ankle jerk	Assess for upper and lower limb reflexes

8.3. Adverse Events and Serious Adverse Events

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

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

Investigators must document their review of each laboratory safety report.

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

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, study device, and/or study procedure and the AE.

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

8.3.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received the investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving the investigational product, the SAE should be reported to the sponsor according to SAE reporting requirements and timelines (see Section 8.3.3) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the CRF.

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

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

8.3.2. Suspected Unexpected Serious Adverse Reactions

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

8.3.3. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the Schedule of Activities (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF and not on the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately, and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of data being available.

Investigators are not obligated to actively seek AE or SAE data after conclusion of the study participation. 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/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.4. Method of Detecting AEs and SAEs

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

8.3.5. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow up each patient at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (Section 8.3.8), will be followed up until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up as defined in Section 7.3.

8.3.6. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator of an SAE to the sponsor 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 comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.7. Pregnancy

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of lasmiditan dosing and until at least 1 month following the last dose of lasmiditan.

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, such as the following, are also considered SAEs:

- spontaneous abortion

- fetal death
- stillbirth
- congenital anomalies
- ectopic pregnancy.

8.3.8. Safety Topics of Interest

In addition to those identified above, the following safety topics of interest will be monitored:

- Cardiovascular safety
- Hepatic safety
- Neurologic effects, including injuries and accidents secondary to neurologic AEs
- Road traffic accidents
- Abuse potential.

8.3.9. Complaint Handling

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

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

8.4. Treatment of Overdose

This is a single-dose study. This section is not applicable for this study.

8.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities, venous blood samples of a maximum of 2 mL each will be collected to determine the plasma concentrations of lasmiditan. An indwelling catheter is recommended for blood collection on Day 1. Patients who choose to go home after the 12-hour assessments will have the catheter removed prior to leaving the site.

Timing of PK samples collected after lasmiditan dosing was determined by applying a D-optimality algorithm to the adult popPK model, which was scaled for pediatric population. Patient burden and other factors were also taken into consideration.

One additional sample may be collected at an additional time point during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

8.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of lasmiditan will be assayed using a validated liquid chromatography with tandem mass spectrometry method.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following the last patient visit for the study.

8.6. Pharmacodynamics

This section is not applicable for 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. Health Economics

This section is not applicable for this study.

9. Statistical Considerations and Data Analysis

9.1. Statistical Hypotheses

No inferential statistical analyses are planned for this study.

9.2. Sample Size Determination

Cohort 1

Approximately 13 patients may be enrolled to obtain at least 11 patients with evaluable PK data for the primary cohort (body weight between 15 kg and 40 kg, inclusive). Patients who do not have evaluable PK data may be replaced.

From the popPK analysis in adults, the interpatient coefficient of variation (CV) was estimated to be 43% for C_{max} and 39% for AUC. Assuming the CV of total variability is not larger than 45%, 11 pediatric patients will provide at least 80% coverage probability that the 95% confidence intervals (CIs) for the geometric mean of these key PK parameters will be within 70% and 140%. The CV for apparent total body clearance and apparent central volume of distribution are similar to those of C_{max} and AUC and, therefore, the precision of estimates for these parameters are expected to be sufficient (Wang et al. 2012).

Cohort 2

Approximately 8 patients may be enrolled to obtain at least 6 patients with evaluable PK data for the secondary cohort (body weight >40 kg and ≤55 kg). This sample size is customary for Phase 1 studies evaluating PK, safety, and tolerability, and is not powered on the basis of statistical hypothesis testing.

Efforts will be made to enroll male and female patients of varying body weights across the weight range defined for the primary and secondary cohorts.

9.3. Populations for Analyses

9.3.1. Patient Disposition

A detailed description of patient disposition will be provided at the end of the study.

9.3.2. Patient Characteristics

For each cohort, age, sex, weight, height, body mass index, race, and other patient demographic characteristics will be summarized using descriptive statistics.

Patient characteristics may be summarized by region (Japanese vs. non-Japanese), if appropriate.

9.4. Statistical Analyses

Statistical analysis of this study will be the responsibility of Lilly or its designee.

Pharmacokinetic analyses will be conducted on data from all patients who receive a dose of the investigational product and have evaluable PK data.

Safety analyses will be conducted for all enrolled patients who receive a dose of the investigational product, whether or not they completed all protocol requirements.

Data analyses will be presented by body weight category, age, body surface area, and glomerular filtration rate.

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

9.4.1. Safety Analyses

Safety analyses will be conducted based on safety data obtained from the screening, PK/safety assessment, and follow-up/early discontinuation phases of the study.

9.4.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure-related AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

Adverse events will be classified by the most suitable term from the most current Medical Dictionary for Regulatory Activities (MedDRA) version.

The incidence of TEAEs will be presented by severity and by association with investigational product as perceived by the investigator. AEs reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study.

All SAEs will be reported and classified by the most suitable term from the most current MedDRA version.

9.4.1.2. Statistical Evaluation of Safety

Safety parameters for analysis will be:

- AEs (including clinically significant ECGs)
- clinical laboratory parameters
- vital signs
- C-SSRS assessments
- Cogstate Pediatric Brief Battery parameters.

The parameters will be listed, and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

Safety parameters may be summarized by region (Japanese vs. non-Japanese), if appropriate.

9.4.2. Pharmacokinetic Analyses

9.4.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for lasmiditan will be calculated by standard noncompartmental methods of analysis from plasma lasmiditan concentrations, and listed and summarized using descriptive statistics.

The primary parameters for analysis will be C_{max}, t_{max}, and AUC of lasmiditan.

Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported.

In addition to estimates of geometric means, the corresponding 95% CIs will also be determined.

Pharmacokinetic parameters may be summarized by region (Japanese vs. non-Japanese) if appropriate.

Additional analysis will be performed if warranted upon review of the data.

9.4.3. Data Review during the Study

Safety and PK data will be reviewed on an ongoing basis. Doses may be adjusted when data are available from at least 3 patients with evaluable PK data in the primary cohort. The purpose of the review is to assess safety/tolerability, evaluate PK data, and inform the dosing of subsequent patients. The investigator and the Lilly sponsor team will make the determination regarding dosing, based on their review of the safety and PK data. If lasmiditan plasma concentrations are unexpected relative to PK predictions, then the dose may be adjusted. Additional reviews may be performed, as deemed appropriate.

9.5. Interim Analyses

Because all patients in a cohort receive the same treatment, review of nonfinal data is not considered an interim analysis. Therefore, there will be no interim analyses in this study.

9.6. Data Monitoring Committee

An external data monitoring committee (DMC) will be used for this study. The DMC will review safety data on an ongoing basis concurrent with team and investigator reviews.

10. Supporting Documentation and Operational Considerations

10.1. 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:

1. consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. applicable International Council for Harmonisation (ICH) GCP Guidelines
3. applicable laws and regulations.

Some of the obligations of the sponsor will be assigned to a third party organization.

Ethical Review

The investigator or appropriate local representative must give assurance that the ethical review board (ERB) was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol, the ICF, and Assent Form must be provided to Lilly before the study may begin at the investigative sites. Lilly or its representatives must approve the ICF before it is used at the investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

The study site's ERB(s) should be provided with the following:

- the current IB and updates during the course of the study
- ICF and Assent Form
- relevant curricula vitae.

10.1.2. Informed Consent

The investigator is responsible for:

- ensuring that the patient or patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICF prior to the performance of any protocol procedures and prior to the administration of investigational product.

- answering any questions the patient or patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if capable.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the investigator. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities.

10.1.4. Protocol Signatures

The sponsor's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

10.1.5. Final Report Signature

The final report coordinating investigator or designee will sign the clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

The sponsor's responsible medical officer and statistician will sign/approve the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

10.1.6. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, or fax
- review and verify data reported to detect potential errors.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

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

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 Lilly data warehouse.

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

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the sponsor.

10.1.7. Study and Site Closure

10.1.7.1. Discontinuation of Study Sites

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

10.1.7.2. Discontinuation of the Study

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

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12. Appendices

Appendix 1. Abbreviations and Definitions

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE 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
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and potential risks involved in participating in a study (required by some institutional review boards [IRBs]/ethical review boards [ERBs]).
AST	aspartate aminotransferase
AUC	area under the concentration-versus-time curve
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum observed drug concentration
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 the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
CRF	case report form
CRP	Clinical Research Physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist (CRS), global safety physician, or other medical officer.
CRU	Clinical Research Unit
C-SSRS	Columbia-Suicide Severity Rating Scale

CV	coefficient of variation
eCOA	electronic Clinical Outcome Assessment
eCRF	electronic case report form
EDC	electronic data capture
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IRB	institutional review board
Legal Representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
MedDRA	Medical Dictionary for Regulatory Activities
open label	A study in which there are no restrictions on knowledge of treatment allocation; therefore the investigator and the study participant are aware of the drug therapy received during the study.
PK	pharmacokinetic(s)

popPK	population pharmacokinetic
randomize	the process of assigning patients to an experimental group on a random basis
SAE	serious adverse event
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.
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TEAE	treatment-emergent adverse event: Any 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 to reach maximum observed drug concentration
ULN	upper limit of normal

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium
Mean cell hemoglobin concentration	Phosphorus
Leukocytes (WBC)	Magnesium
Platelets	Glucose (random)
Absolute counts of:	Blood urea nitrogen (BUN)
Neutrophils	Total protein
Lymphocytes	Albumin
Monocytes	Total bilirubin
Eosinophils	Direct bilirubin
Basophils	Total protein
	Alkaline phosphatase (ALP)
Urinalysis[a]	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	Uric acid
Protein	Estimated glomerular filtration rate (eGFR)[b]
Glucose	Creatinine
Ketones	
Bilirubin	
Urobilinogen	
Blood	**Other Tests**
Nitrite	Urine drug screen[a]
Leukocyte esterase[c]	Urine pregnancy test[d]
Urine culture[c]	Serum pregnancy test[a]
Microsopic analysis[c]	Gonadal hormone[a] (estradiol for females, and testosterone for males)

Abbreviations: RBC = red blood cell; WBC = white blood cell.

[a] Assayed by sponsor-designated laboratory.

[b] GFR calculated by Bedside Schwartz 2009 formula or the Japanese Society for Pediatric Nephrology formula for patients in Japan.

[c] A positive urine leukocyte esterase result will require a follow-up sample with microscopic analysis and possibly a urine culture.

[d] Performed locally.

Note: Additional tests may be performed at the discretion of the investigator as needed.

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-LAHX Sampling Summary

Purpose	Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Total Volume (mL)
Hematology[a]	2	3	6
Chemistry[a]	2.5	3	7.5
Gonadal hormones	3.5	1	3.5
Serum pregnancy test[a,b]	0	1	0
Pharmacokinetics	2	9	18
Blood discard for cannula patency	1	9	9
Total			44
Total for clinical purposes rounded up to nearest 10 mL			50
Hepatic monitoring[c]			3-30

[a] Additional samples may be drawn if needed for safety purposes.

[b] Sample volume included with chemistry or gonadal hormones test volume.

[c] Unscheduled hepatic monitoring testing may be performed as part of patient follow-up, based on laboratory safety values and in consultation with Lilly CRP/CRS.

Appendix 3. 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 patients in consultation with Lilly Medical or its designee.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin time
WBC	Prothrombin time, INR
Neutrophils	
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
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin**
CPK	**antibody)[a]**

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

a Assayed by Lilly-designated or central laboratory.

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

Leo Document ID = d443c63b-d4f7-4e9e-841a-ea05c0a724fe

Approver: PPD
Approval Date & Time: 28-Mar-2019 18:18:07 GMT
Signature meaning: Approved

Approver:PPD
Approval Date & Time: 29-Mar-2019 02:36:10 GMT
Signature meaning: Approved