

H8H-MC-LAHW Statistical Analysis Plan Version 1

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

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Approval Date: 10-Jun-2020

1. Statistical Analysis Plan: H8H-MC-LAHW: A Phase 3, Open-Label Study of Lasmiditan in Pediatric Patients with Migraine – PIONEER-PEDS2

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Lasmiditan (LY573144) Acute Migraine Treatment

Study H8H-CD-LAHW is a prospective, randomized, open-label, 12-month study to assess safety in children and adolescents with a diagnosis of migraine who previously enrolled in and completed Study H8H-MC-LAHX or H8H-MC-LAHV.

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Protocol H8H-CD-LAHW
Phase 3**

Statistical Analysis Plan electronically signed and approved by Lilly on date provided below.

Approval Date: 10-Jun-2020 GMT

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3. Revision History

Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit (FPV). This study is open-label, therefore, unblinding occurs at FPV.

4. Study Objectives

Table LAHW.4.1 and Table LAHW.4.2 provide the protocol defined primary and secondary objectives.

The estimand (ICH E9 R1 2019) associated with each endpoint/analysis is documented in the following places:

- The population of interest is described in the protocol inclusion/exclusion criteria in Section 6.2.
- The endpoints may be found in Table LAHW.4.1 and Table LAHW.4.2.
- The handling of intercurrent events and missing data may be found in Section 6.4 and Table LAHW.6.5 of this document.
- Summary measures are described in Table LAHW.6.5 and Table LAHW.6.6.

4.1. Primary Objective

Table LAHW.4.1 shows the primary objectives and endpoints of the study.

Table LAHW.4.1. Primary Objectives and Endpoints

Objective	Endpoint
To evaluate the safety and tolerability of long-term intermittent use of lasmiditan for the acute treatment of migraine in pediatric patients.	• Nature, proportion, and severity of TEAEs by treated attack. • Proportion of discontinuation due to AEs.

Abbreviations: AE = adverse event; TEAE = treatment-emergent adverse event.

4.2. Secondary Objectives

Table LAHW.4.2 shows the secondary objectives and endpoints of the study for the overall population.

Table LAHW.4.2. Secondary Objectives and Endpoints

Objectives	Endpoints
To evaluate the efficacy of intermittently dosed lasmiditan in the treatment of multiple migraine attacks over time in pediatric patients.	• Proportion of treated attacks with pain freedom at 2 hours after dosing for each 3-month period. • Proportion of treated attacks with pain relief at 2 hours after dosing for each 3-month period. • Proportion of treated attacks with MBS freedom at 2 hours after dosing for each 3-month period.

Abbreviation: MBS = most bothersome symptom.

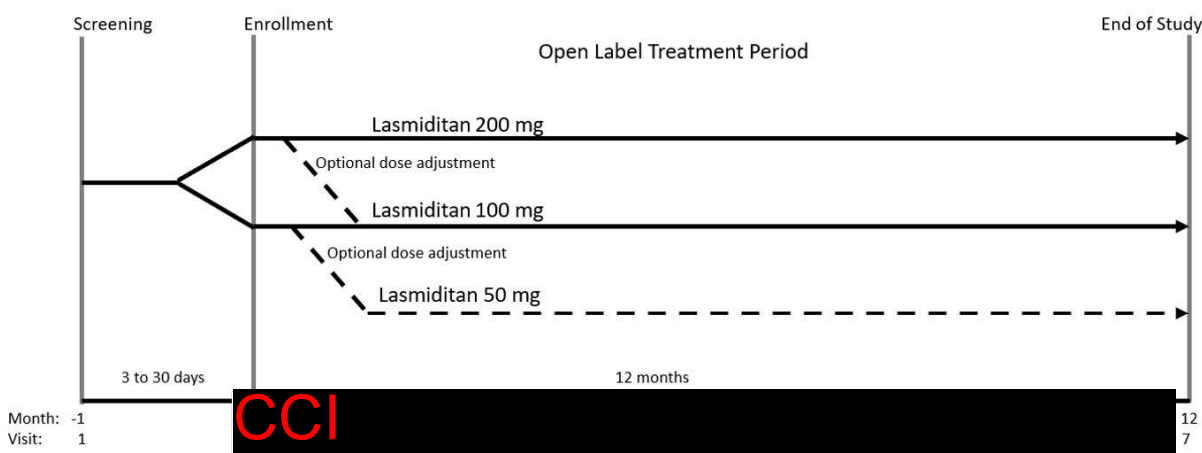
5. Study Design

5.1. Summary of Study Design

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

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

Study participant visits to the clinic are scheduled at [redacted] and 12 months after study enrollment. Figure LAHW.5.1 illustrates the design.



Abbreviation: mg = milligrams.

Figure LAHW.5.1. Illustration of study design for clinical protocol H8H-MC-LAHW.

5.2. Determination of Sample Size

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

5.3. Method of Assignment to Treatment

Participants will be stratified by age group (6 to <[REDACTED] years and [REDACTED] to <18 years based on age at time of screening into Study LAHX or LAHV) and randomized in a [REDACTED] ratio at study entry to treatment with [REDACTED] doses corresponding to the 100 mg and 200 mg adult exposure (referred to throughout as lasmiditan 100 mg and lasmiditan 200 mg). The lasmiditan exposure may be reduced 1 time during study participation in the event of tolerability concerns, after treatment of at least 3 migraine attacks at the randomized exposure. Study participants may use lasmiditan to treat [REDACTED] migraine attacks [REDACTED] on an outpatient basis.

Table LAHW.5.1 shows the planned treatment regimens [REDACTED]. The 50 mg exposure group will only be used if patients randomized to the 100 mg exposure group require a reduction due to tolerability issues; 50 mg exposure is not a randomized exposure group.

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6. A Priori Statistical Methods

6.1. General Considerations

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or designee. SAS[®] software will be used to perform all statistical analyses.

Unless otherwise specified, safety, efficacy, and medical resource utilization, and health economics analyses will be conducted on the evaluable population.

The following terminology will be applied:

- **Treatment group** is defined as the exposure group (lasmiditan 50 mg, lasmiditan 100 mg, or lasmiditan 200 mg) the patient is assigned to for treatment of migraine attacks. Patients are initially randomized to either the lasmiditan 100 mg or lasmiditan 200 mg treatment group and may reduce their treatment group at 1 time during the study. Therefore, a patient may be subsequently be assigned to the lasmiditan 50 mg or the lasmiditan 100 mg treatment group. See Section 5.3 for further details.
- **Dose** is defined as the tablet strength dispensed to the patient, CCI, in order to achieve the exposure for the assigned treatment. See Section 5.3 for further details.

Table LAHW.6.1 gives the treatment group descriptions to be displayed for each analysis population.

Table LAHW.6.1. Treatment Group Descriptions by Analysis Populations

Analysis Population	Study Period/s	Summary	Treatment Group Description	Abbreviation
Randomized Population	Open Label Treatment	All summaries	Randomized to Lasmiditan 100 mg	LTN 100mg
			Randomized to Lasmiditan 200 mg	LTN 200mg
			All Lasmiditan	All LTN
Evaluable Population	Open Label Treatment and EOS	• by attack • by visit	Lasmiditan 50 mg	LTN 50mg
			Lasmiditan 100 mg	LTN 100mg
			Lasmiditan 200 mg	LTN 200mg
			All Lasmiditan	All LTN
		• by patient	Randomized to Lasmiditan 100 mg	LTN 100mg
			Randomized to Lasmiditan 200 mg	LTN 200mg
			All Lasmiditan	All LTN

Abbreviations: All LTN = total of all lasmiditan treatment groups; LTN = lasmiditan; mg = milligram.

As specified throughout, analyses will be summarized by treated migraine attack, by patient, or by visit. The sections below describe each type of summary.

6.1.1. *Summaries by Treated Migraine Attack*

Summaries by treated migraine attack will be by treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg).

Baseline will be defined as the assessment recorded in the CCI at the time of study medication for each attack.

6.1.2. *Summaries by Patient*

Summaries by patient will be respective to the randomized treatment group (lasmiditan 100 mg and lasmiditan 200 mg) at study enrollment. Patients who reduce their dose due to tolerability will be included in the initially randomized treatment group.

Baseline will be defined as the last assessment prior to the first dose of lasmiditan. Specifically, baseline will be obtained from the parent study (LAHX or LAHV) for patients who received at least 1 dose of lasmiditan in the parent study, otherwise, baseline will be obtained from Study LAHW. The baseline period is defined as the start of screening and ends prior to the first dose of lasmiditan either from the parent study or from Study LAHW.

6.1.3. *Summaries by Visit*

Summaries by visit will be respective to the treatment group (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) corresponding to the patient's most recent treatment

Baseline will be defined as the last assessment prior to the first dose of lasmiditan. Specifically, baseline will be obtained from the parent study (LAHX or LAHV) for patients who received at least 1 dose of lasmiditan in the parent study, otherwise, baseline will be obtained from Study LAHW.

6.2. Analysis Populations

Table LAHW.6.2 describes the analysis populations for Study LAHW. A summary of each population will be provided by treatment group.

Table LAHW.6.2. Populations for Analysis.

Population	Description
Enrolled	All patients who sign informed consent.
Randomized	All patients randomized to study medication. Patients will be evaluated by the treatment group to which they are randomized.
Evaluable	All randomized patients who administer at least 1 dose of study medication. Patients will be included in the treatment group (LTN 50 mg, LTN 100 mg, or LTN 200 mg) respective to the treatment they receive.
CCI	
12-Month Exposure Population	All randomized patients who participate in study LAHW for at least 12 months (348 days) and treat 12 or more migraine attacks over their participation in the study.

Abbreviations: LTN = lasmiditan; mg = milligrams.

6.3. Adjustments for Covariates

No inferential statistical analyses are planned, therefore, no adjustments for covariates will be included.

6.4. Handling of Dropouts or Missing Data

6.4.1. Observed Data

Secondary and exploratory efficacy analyses will be summarized using the observed data with the following exceptions:

- Efficacy data will be censored following the administration of additional migraine medication for rescue for the corresponding migraine attack. Patients who have a missing or incomplete time associated with their rescue medication will be censored immediately following dosing.

This method may be justified when the estimand of interest uses the hypothetical and composite strategies (ICH E9 R1 2019) for handling intercurrent events. In this strategy, the scientific question of interest is to summarize the effect of lasmiditan in a hypothetical scenario where all patients have complete data for the composite measure of (1) achieving the endpoint of interest (i.e., pain freedom) and (2) without the use of additional migraine medication for rescue.

6.4.2. Nonresponder Imputation (NRI)

A supportive analyses for pain freedom at 2-hours post dose will be performed using a nonresponder imputation (NRI). The NRI will classify patients with missing data or who treat their migraine with additional migraine medication for rescue as nonresponders.

The NRI method is justified when the estimand of interest uses the composite strategy (ICH E9 R1 2019) for handling intercurrent events. In this strategy, patients with any intercurrent event that leads to missing data or the use of additional migraine medication for rescue are classified as nonresponders for all subsequent time points. Therefore, using a composite estimand

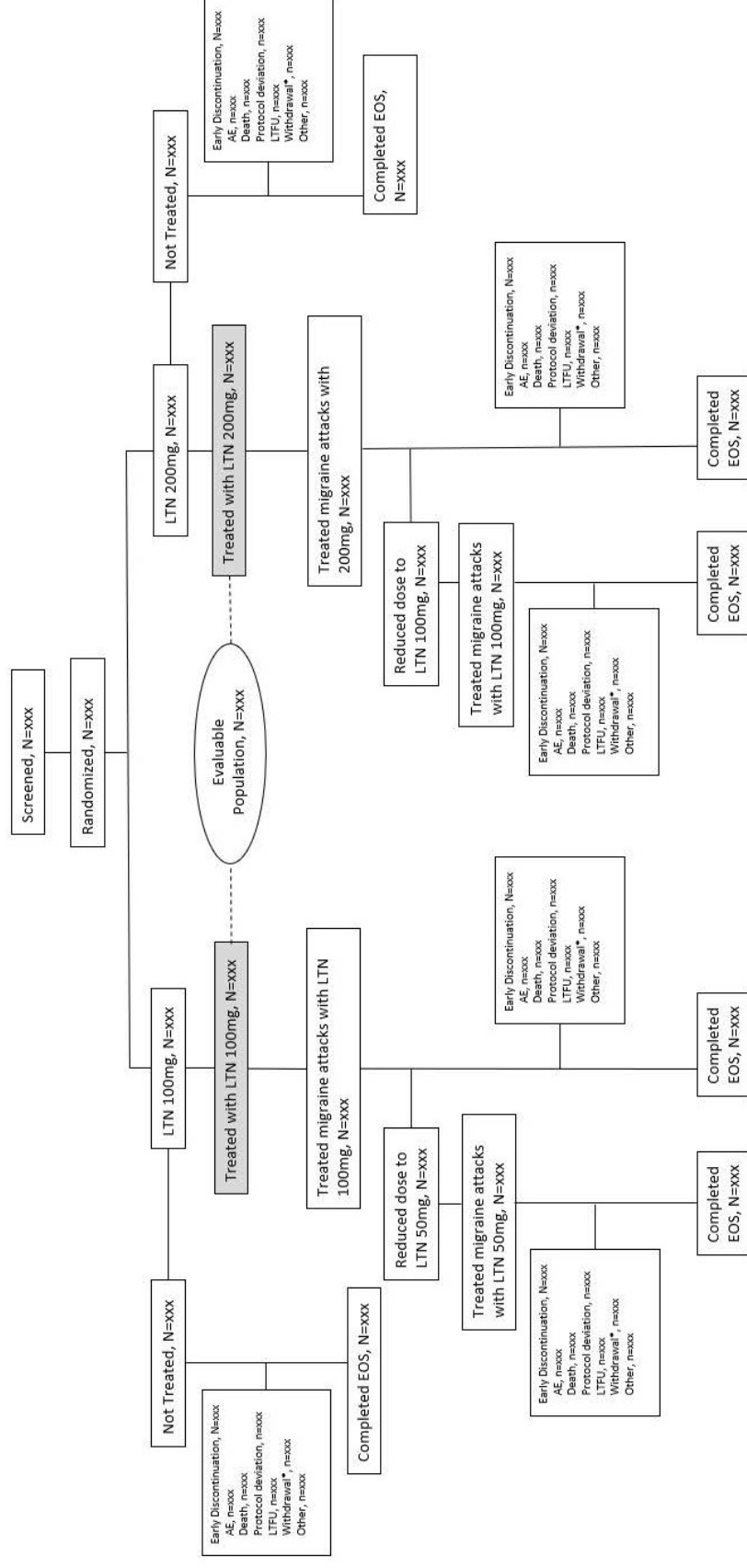
approach, no data would be missing and the scientific question of interest is to summarize the effect of lasmiditan for the composite measure of (1) achieving the endpoint of interest (i.e., sustained pain freedom) and (2) remaining in the study, adherence to data collection procedures, and without the use of additional migraine medication for rescue.

6.5. Patient Disposition

Patients will be summarized as illustrated in [Figure LAHW.6.1](#). Additionally, the number and percent of patients in the CCI and 12-month exposure populations will be summarized.

A summary of patients enrolled at each investigative site and country will be provided.

Patient disposition for the enrolled population will be presented in a listing.



Abbreviations: EOS = end of study; LTN = lasmiditan.

* Reasons for withdrawal include sponsor decision, physician decision, patient decision, and parent/guardian decision.

Figure LAHW.6.1. **Disposition.**

6.6. Patient Characteristics

6.6.1. Demographics

The following demographics and baseline patient characteristics (last available assessment for either Screening/Visit 1 or CCI of Study LAHW) will be summarized for the evaluable population:

- Age (years)
- Age groups:

CCI

- Height (cm)
- Weight (kg)
- Weight group CCI
- Body mass index (BMI) ($\text{weight (kg)} / [\text{height (m)}]^2$)
- Geographic region (North America, Europe, Other)
- Parent study:
 - LAHX
 - LAHV
- Preventive treatment of migraine use (yes, no)
- Menstrual status for female patients (pre-menarchal, menarchal)
- Pubertal status (pre-pubertal, pubertal)
- Disability (PedMIDAS total score)

Age will be calculated using the difference in days between the date of birth and the date of informed consent. For sites that prohibit date of birth collection by privacy law, age will be imputed as follows:

- If month and year are reported, age will be the difference in days between the first day of the month and year of birth and the date of informed consent.
- If only year is reported, age will be the difference in days between July 1st of the year of birth and the date of informed consent.

Height is collected in triplicate; the reported height will be calculated as the average of the 3 collected measurements.

For patients taking migraine preventive medication, treatment regimen is stable and has been taken for at least 3 months prior to Visit 1. Preventive treatments include documented use of one or more of the following concomitant medications:

- propranolol
- topiramate
- cinnarizine
- amitriptyline.

These medications are included as having some evidence to support their use as preventive medications for migraines in the American Academy of Neurology and American Headache Society Practice Parameter (Szperka et al. 2019).

The following demographics and baseline patient characteristics (Screening/Visit 1 of the parent study) will also be summarized:

- Age (years)
- Age groups:

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- Sex (male, female)
- Race (American Indian or Alaska native, Asian, black or African American, white, native Hawaiian or other pacific islander, multiple, other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, unknown, N/A)
- Duration of migraine history (years)
- Average number of migraine attacks per month during the past 2 months
- For patients who participated in study LAHV:
 - History of migraine with aura (yes, no)
 - History of migraine without aura (yes, no)
 - Average duration of an untreated migraine attack (hours)

Duration of migraine history, presented in years, will be calculated using the difference in days between the date of migraine diagnosis and the date of informed consent.

All demographic data will be presented in a listing for the enrolled population.

6.6.2. Medical History

Medical history and pre-existing conditions will be coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA). Medical history is defined as the combination of 1) any medical history collected in the parent study and 2) any illness(es) that are new since participation in the parent study and end prior to the signing of informed consent. Pre-existing conditions are those events ongoing at the time of CCI. For the evaluable population, medical history and pre-existing conditions will be summarized by treatment group. MedDRA preferred terms (PTs) will be listed by decreasing frequency in the lasmiditan 200 mg treatment group and nested within system organ class (SOC) where SOCs will be listed alphabetically. Patients with multiple occurrences of the same medical history term will be counted once within the corresponding SOC and PT.

6.6.3. Migraine Treatment History

Medication history will be captured for both current and previous treatment and will be coded using the most current version of the World Health Organization (WHO) Drug Dictionary. Migraine treatment history, including acute and preventive treatments, will be summarized for the evaluable population by treatment group using WHO PTs listed by decreasing frequency in

the lasmiditan 200 mg treatment group. Patients with multiple occurrences of the same medication will be counted once within the corresponding PT.

6.6.4. Characteristics of Treated Migraine Attacks

Characteristics of treated migraine attacks will be summarized for the evaluable population and presented by the following timepoints:

- quarterly: 0 to 3 months, >3 to 6 months, >6 to 9 months, >9 to 12 months
- CCI [REDACTED]
- 0 to 12 months

The following will be summarized by treated migraine attack:

- Baseline migraine severity
 - Severe
 - Moderate
 - Mild
 - None
- Baseline associated symptoms
 - Nausea
 - Phonophobia
 - Photophobia
 - None
- Baseline most bothersome symptom (MBS)
 - Nausea
 - Phonophobia
 - Photophobia
- Time of day
 - Morning (06:00 to 11:59)
 - Afternoon (12:00 to 17:59)
 - Evening (18:00 to 23:59)
 - Overnight (00:00 to 05:59)
- Day of week
 - Weekday
 - Weekend
- Other medications taken to treat migraine (yes or no)
 - No
 - Yes, before 2-hour assessment
 - Yes, after 2-hour assessment

6.7. Drug Accountability/Compliance

Study drug is administered by the patient on an as needed basis (PRN). The patient will record, in the CCI [REDACTED], each instance (date, time) they take lasmiditan.

At each postbaseline study visit, the patient will return any unused study medication. The number of tablets dispensed and returned will be reconciled against the record in the CCI [REDACTED].

Study drug compliance will be calculated as a percent for each patient as follows:

$$100 \cdot \frac{(\text{total \# tablets dispensed} - \text{total \# tablets returned})}{\text{total \# recorded lasmiditan doses}}$$

A patient is considered compliant if their compliance is 100%. The number and proportion of patients who are considered study drug compliant will be summarized by treatment group for the evaluable population.

Study drug compliance data will also be presented in a listing. The listing will also include drug compliance as assessed by the investigator ('less than prescribed', 'within the limits defining intended compliance relative to the amount prescribed', and 'more than prescribed') along with a reason if 'less than prescribed' or 'more than prescribed' was selected.

Additionally, a listing of treatment assignments including dose adjustments, if applicable, will be presented for the enrolled population.

6.8. Concomitant Therapy

Concomitant medications are those taken during the study, from the screening visit (Visit 1) to end of study (EOS) visit. Missing medication start date/time and stop date/time will be imputed by following the rules in [Appendix 1](#). After the imputation rules are applied, if the reported medication still has a missing start date/time and/or end date/time it will be considered as concomitant.

The number and proportion of patients with concomitant medication use will be summarized by treatment group for the evaluable population. Medications will be coded using the most current version of the WHO Drug Dictionary and sorted by decreasing frequency of PTs in the lasmiditan 200 mg group.

6.9. Safety Analyses

All safety analyses will be performed on the evaluable population. Safety assessments will be collected via **CCI** or the case report form (CRF).

Safety will be assessed by summarizing and analyzing the following:

- extent of exposure;
- AEs, including, treatment-emergent AEs (TEAEs) and serious AEs (SAEs);
- laboratory evaluations (chemistry, hematology, and urinalysis);
- vital signs (blood pressure [BP], pulse, and body temperature);
- **CCI**
- cognition (Cogstate Pediatric Brief Battery);
- growth and development (height, weight, menstrual status for females, and pubertal status);
- safety topics of interest.

Categorical data will include sample size (total number of treated migraine attacks or total number of patients), frequency counts, proportions, and 95% confidence intervals (CIs) for the

proportion. Treatment group comparisons (lasmiditan 200 mg versus lasmiditan 100 mg) will also be performed for the by patient analyses using a Fisher's exact test. Continuous data will include the sample size (total number of patients), mean, standard deviation (SD), minimum, median, and maximum. Change from baseline will be calculated as the postbaseline value minus the baseline value. Change from baseline analyses will include patients who have a baseline and a postbaseline assessment.

6.9.1. Extent of Exposure

Extent of exposure will be summarized for the following timepoints for the evaluable population:

- quarterly: 0 to 3 months, >3 to 6 months, >6 to 9 months, >9 to 12 months
- 0 to 12 months

The following summaries will be conducted by patient:

- average number of treated migraine attacks
- average number of treated migraine attacks per month
- proportion of patients who treated at least 1 migraine attack
- proportion of patients who treat, on average, at least 1 migraine attack per month
- duration of time (months) in study

6.9.2. Adverse Events

6.9.2.1. Definitions

Adverse events are defined as follows:

- any untoward medical occurrences in a patient treated with lasmiditan, whether or not such events are related to study drug, and
- occurring after signing the informed consent/assent.

Adverse events will be classified based upon the latest version of MedDRA.

Treatment-emergent adverse events are defined as reported AEs that first occurred or ongoing events that worsen in severity within 48 hours after dosing with lasmiditan. For each TEAE, the reported severity level of the event will be determined by patient or physician opinion. Adverse events that are missing severity will be considered treatment-emergent if they occurred within 48 hours after dosing with lasmiditan. The MedDRA Lowest Level Term (LLT) will be used in the treatment-emergent computation.

An SAE is any AE 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.

6.9.2.2. Analyses

All AE analyses will be summarized by treated migraine attack and by patient except for AEs that lead to study discontinuation which will only be summarized by patient.

In an overview table, AEs, TEAEs (including by maximum severity), SAEs, deaths, and AEs that lead to discontinuation of lasmiditan will be summarized for the evaluable population.

The following will be summarized for the evaluable population using MedDRA PTs listed by decreasing frequency in the lasmiditan 200 mg treatment group:

- AEs
- TEAEs
- TEAEs, nested within SOC, where SOC will be listed alphabetically
- TEAEs by maximum severity (Maximum severity for the MedDRA PT is the maximum postbaseline severity observed from all associated LLTs mapping to the MedDRA PT, where the severity is available. For each LLT, the maximum severity at baseline will be used as the baseline severity. AEs with a missing severity at baseline will be treated as “mild” in severity. If all severities are missing for the defined postbaseline period of interest, it will be reported as missing in the table).
- TEAEs that are related to study drug
- SAEs
- SAEs that are related to study drug
- AEs, including TEAEs, that lead to discontinuation of lasmiditan

For events that are gender-specific, the denominator and computation of the proportion will include only patients or treated migraine attacks from the specific gender.

Missing dates/times are imputed in accordance with [Appendix 1](#).

All SAEs will be presented in a listing for the enrolled population.

6.9.3. Clinical Laboratory Evaluation

Clinical laboratory parameters are collected at Screening (Visit 1), CCI [REDACTED], and Month 12 (Visit 7) and are not temporally related to lasmiditan dosing. Summaries for laboratory parameters will be performed by visit. Age appropriate normal laboratory ranges and clinical measurements will be used.

Box and whisker plots for observed and change from baseline values for laboratory parameters will be presented by treatment group and visit for the evaluable population.

In addition, the number and proportion of patients with treatment-emergent high or low results based on age appropriate reference ranges will be summarized by treatment group and visit for each parameter for the evaluable population. A low result is defined as a change from a value

greater than or equal to the low limit at baseline to a value less than the low limit at any postbaseline visit. A high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater than the high limit at any postbaseline visit. Scheduled visits, unscheduled visits, and repeat measurements will be included.

Treatment-emergent abnormal laboratory results, including high and low results, will be presented in a listing for the enrolled population.

6.9.4. Vital Signs

Vital signs are collected at Screening (Visit 1), CCI, and Month 12 (Visit 7) and are not temporally related to lasmiditan dosing. Age appropriate normal ranges will be used.

Box and whisker plots for observed and change from baseline values for vital sign parameters will be presented by treatment group and visit for the evaluable population.

Vital signs include systolic BP and diastolic BP (mm Hg), pulse (bpm), and temperature (°F). Blood pressure and pulse measurements will be taken when the patient is in a sitting position. Vital signs will consist of 1 pulse, 1 temperature, and 3 BP measurements. The 3-sitting BP measurements will be averaged and used for the analysis. Observed values and change from baseline values will be summarized by treatment group and visit for each parameter for the evaluable population.

Shift tables will be produced for the evaluable population in accordance with the age appropriate Lilly-defined criteria displayed in [Table LAHW.6.3](#). Scheduled visits, unscheduled visits, and repeat measurements will be included.

Table LAHW.6.3. Criteria for Shifts in Vital Signs

Parameter	Age Group	Direction	Criteria	Baseline Criteria
Systolic BP (mm Hg) (sitting)	6-9	Low	≤ 80 and decrease ≥ 15	> 80
		High	≥ 119 and increase ≥ 15	< 119
	10-12	Low	≤ 85 and decrease ≥ 20	> 85
		High	≥ 126 and increase ≥ 20	< 126
	13-17	Low	≤ 90 and decrease ≥ 20	> 90
		High	≥ 129 and increase ≥ 20	< 129
Diastolic BP (mm Hg) (sitting)	6-9	Low	≤ 45 and decrease ≥ 10	> 45
		High	≥ 78 and increase ≥ 10	< 78
	10-12	Low	≤ 50 and decrease ≥ 10	> 50
		High	≥ 82 and increase ≥ 10	< 82
	13-17	Low	≤ 50 and decrease ≥ 10	> 50
		High	≥ 86 and increase ≥ 10	< 86
Pulse (bpm) (sitting)	6-9	Low	< 60 and decrease ≥ 25	≥ 60
		High	> 150 and increase ≥ 25	≤ 150
	10-12	Low	< 60 and decrease ≥ 25	≥ 60
		High	> 140 and increase ≥ 25	≤ 140
	13-17	Low	< 50 and decrease ≥ 15	≥ 50
		High	> 120 and increase ≥ 15	≤ 120

Abbreviations: BP = blood pressure; bpm = beats per minute; mm Hg = millimeters of mercury.



6.9.6. Cognition

6.9.6.1. Possible Effects on Mental Ability

Adverse events and TEAEs that represent possible effects on mental ability (see [Appendix 2](#)) will be summarized by treated migraine attack and by patient for the evaluable population using PTs from the latest version of MedDRA nested within SOC, where SOCs will be listed alphabetically.

6.9.6.2. Cogstate Pediatric Brief Battery

The Cogstate Pediatric Brief Battery (© 2018 Cogstate Ltd.) is administered at Screening in the parent study, **CCI** and Month 12 (Visit 7). The Cogstate Pediatric Brief Battery includes of 4 tests (see [Table LAHW.6.4](#)):

Table LAHW.6.4. The Four Cogstate Pediatric Brief Battery Tests

Test	Cognitive Domain	Calculation of Test Score	Interpretation
Detection Test	Psychomotor Function	Reaction time defined as the mean of the log10 transformed reaction times for correct responses	Lower score is defined as better performance
Identification Test	Attention	Reaction time defined as the mean of the log10 transformed reaction times for correct responses	Lower score is defined as better performance
One Card Learning Test	Visual Learning	Accuracy defined as the arcsine of the square root of proportion of correct responses	Higher score is defined as better performance
One Back Test	Working Memory	Reaction time defined as the mean of the log10 transformed reaction times for correct responses	Lower score is defined as better performance

Summaries may be performed by the following exposure groups (these groups could be adjusted based on actual data):

- Treated, on average, 1 attack per month
- Treated, on average, 2 attacks per month
- Treated, on average, 3 attacks per month
- Treated, on average, >3 attacks per month

Observed and change from baseline test scores will be summarized for baseline and postbaseline visits respective to the last dose of lasmiditan the patient received (lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) for the evaluable population. For each test score, the Cohen's d effect size measure (Cohen 1988) for the lasmiditan 100 mg and lasmiditan 200 mg groups will also be computed at each postbaseline visit as follows:

$$d = \frac{mean_{CFB,LTN\ 200mg} - mean_{CFB,LTN\ 100mg}}{SD_{CFB}}$$

where:

- $mean_{CFB,100mg}$ = mean change from baseline for lasmiditan 100 mg treatment group
- $mean_{CFB,200mg}$ = mean change from baseline for lasmiditan 200 mg treatment group
- SD_{CFB} = standard deviation of mean change from baseline values for the pooled lasmiditan 100 mg and lasmiditan 200 mg groups

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

$$RCI = \frac{score_{postbaseline} - score_{baseline}}{s_{norm}\sqrt{2(1-r)}} \times Multiplicand$$

where:

- $score_{postbaseline}$ = patient's score at the given postbaseline visit
- $score_{baseline}$ = patient's score at baseline
- s_{norm} = population standard deviation from age-matched normative data (see [Appendix 3](#))
- r = normative test-retest reliability (see [Appendix 3](#))
- $Multiplicand$ = -1 for the Detection, Identification, and One Back tests
- = +1 for the One Card Learning test

Additionally, the number and proportion of patients with significant cognitive changes will be summarized by visit for the evaluable population (Ingraham and Aiken 1996; Louey et al. 2014). Significant cognitive changes are defined as RCI scores less than or equal to -1.65 in at least 2 of the 4 tests.

6.9.7. Growth and Development

Growth and development parameters are collected at Screening (Visit 1), CCI, and Month 12 (Visit 7). Summaries for growth and development parameters will be performed by visit. Summaries may be performed by the following exposure groups (these groups could be adjusted based on actual data):

- Treated, on average, 1 attack per month
- Treated, on average, 2 attacks per month
- Treated, on average, 3 attacks per month
- Treated, on average, >3 attacks per month

Growth and development parameters include height (cm), weight (kg), and calculated BMI (kg/m^2). Height measurements are performed in triplicate, the 3 measurements will be averaged for the analysis. Observed values, change from baseline values, and standardized values (percentiles and Z-scores) for the parameters will be summarized for each visit for the evaluable population. The standardized values will be estimated from the National Center for Health Statistics (NCHS) growth curve for height, weight, and BMI.

6.9.8. Menstrual and Pubertal Status

6.9.8.1. Menstrual Status

For female patients, the onset of menstruation (yes/no) will be collected at Screening (Visit 1), CCI, and Month 12 (Visit 7). Summaries for menstrual status will be performed by visit for female patients in the evaluable population. Summaries will also include the number and proportion of female patients who shift from pre-menarchal to menarchal.

6.9.8.2. Pubertal Status

Pubertal status will be defined as follows:

- For males, if the testosterone blood hormone level is greater than 20 ng/dl then their pubertal status will be “pubertal”; otherwise their pubertal status will be “pre-pubertal”.
- For females, if the patient reports their menstrual status as “yes” or their estradiol blood hormone level is greater than 20 pg/ml then their pubertal status will be “pubertal”; otherwise their pubertal status will be “pre-pubertal”.

Gonadal hormones are collected at Screening (Visit 1), CCI [REDACTED], and Month 12 (Visit 7). Summaries for pubertal status will be performed by visit for the evaluable population. Summaries will also include the number and proportion of patients who shift from pre-pubertal to pubertal at each postbaseline visit.

6.9.9. Safety Topics of Interest

This section includes areas of interest whether due to observed safety findings, potential findings based on drug class, or requested by a regulatory agency for any reason.

Standardized MedDRA Queries (SMQs) are groupings of terms from one or more MedDRA SOCs that relate to a defined medical condition or area of interest. When an SMQ is specified, the resulting tabular display will include counts and percentages at the SMQ level and at the PT level within the SMQ. When an SMQ involves both narrow and broad terms, the summaries will occur at the SMQ level, then the narrow/broad level, and subsequently the PT level within the SMQ.

6.9.9.1. Cardiovascular Safety

Definitions of Lilly Search Categories (LSCs) for cardiovascular (CV) events:

1. Potential CV AEs: all PTs (for TEAEs and AEs) in the SMQs listed below plus PTs of abdominal pain, abdominal pain upper, and abdominal pain lower.
2. Likely CV AEs: a subset of the potential CV AEs. All clinical information from patients who report the PT events identified from the search described above (for potential CV AEs) will undergo medical review and medical judgment will be applied to determine if the TEAE/AE (for each patient) was likely CV in nature. If so, it will be defined as a likely CV AE.

SMQs:

- broad and narrow terms in cardiac arrhythmias (includes sub SMQs; SMQ 20000049)
- broad and narrow terms in cardiac failure (SMQ 20000004)
- broad and narrow terms in cardiomyopathy (SMQ 20000150)
- broad and narrow terms in central nervous system vascular disorders (includes sub SMQs; SMQ 20000060)
- broad and narrow terms in embolic and thrombotic events (includes sub SMQs; SMQ 20000081)
- broad and narrow terms in hypertension (SMQ 20000147)

- broad and narrow terms in ischemic heart disease (includes sub SMQs; SMQ 20000043)
- broad and narrow terms in pulmonary hypertension (SMQ 20000130)
- broad and narrow terms in Torsade de pointes/QT prolongation (SMQ 20000001)

The following will be summarized (MedDRA PTs will be sorted by decreasing frequency in the lasmiditan 200 mg group) by treated migraine attack and by patient for the evaluable population:

- Potential CV AEs.
- Likely CV AEs.
- Likely CV TEAEs.
- Likely CV SAE by whether they are treatment-emergent or non-treatment-emergent.

6.9.9.2. Hepatic Safety

Hepatic shift tables will be produced for maximum postbaseline elevations from the maximum measurement in the baseline period (Section 6.9) for the evaluable population. Scheduled visits, unscheduled visits, and repeat measurements will be included.

The following shift tables will be produced:

- The proportion of patients with at least one postbaseline alanine aminotransferase (ALT) measurement greater than or equal to 3 times (3x), 5 times (5x), and 10 times (10x) the performing laboratory upper-level of normal (ULN) will be summarized for the following:
 - The analysis of 3x ULN will contain 4 subsets:
 - patients whose maximum baseline value is less than or equal to 1x ULN
 - patients whose maximum baseline is greater than 1X ULN but less than 3x ULN
 - patients whose maximum baseline value is greater than or equal 3x ULN
 - patients whose baseline values are missing
 - The analysis of 5x ULN will be contain 5 subsets:
 - patients whose maximum baseline value is less than or equal to 1x ULN
 - patients whose maximum baseline is greater than 1x ULN but less than 3x ULN
 - patients whose maximum baseline is greater than or equal to 3x ULN but less than 5x ULN
 - patients whose maximum baseline value is greater than or equal to 5x ULN
 - patients whose baseline values are missing
 - The analysis of 10x ULN will contain 6 subsets:
 - patients whose maximum baseline value is less than or equal to 1x ULN
 - patients whose maximum baseline is greater than 1x ULN but less than 3x ULN

- patients whose maximum baseline is greater than or equal to 3x ULN but less than 5x ULN
 - patients whose maximum baseline is greater than or equal to 5x ULN but less than 10x ULN
 - patients whose maximum baseline value is greater than or equal to 10x ULN
 - patients whose baseline values are missing
- The proportion of patients with at least one postbaseline aspartate transaminase (AST) measurement greater than or equal to 3 times (3x), 5 times (5x), and 10 times (10x) the Covance ULN will be summarized for the subsets described above for ALT.
- The proportion of patients with at least one postbaseline serum alkaline phosphatase (ALP) measurement greater than or equal to 2 times (2x) the Covance ULN will be and summarized for the following 4 subsets:
 - patients whose maximum baseline value is less than or equal to 1x ULN
 - patients whose maximum baseline is greater than 1x ULN but less than 2x ULN
 - patients whose maximum baseline value is greater than or equal to 2x ULN
 - patients whose baseline values are missing
- The proportion of patients with at least one postbaseline total bilirubin (TBL) measurement greater than or equal to 2x the Covance ULN will be summarized for the 4 subsets described above for ALP.

6.9.9.3. Injuries and Accidents Secondary to Neurologic Adverse Events

The number and percentage of patients with at least 1 TEAE in the ‘Nervous System Disorders’ SOC and/or at least 1 AE in the ‘Injury, Poisoning, and Procedural Complications’ SOC will be summarized by patient for the evaluable population.

Among patients with at least 1 AE in the ‘Injury, Poisoning, and Procedural Complications’ SOC, the number and percentage of patients who report AEs in this SOC will be summarized by patient using MedDRA PTs listed by decreasing frequency in the lasmiditan 200 mg group. For each AE in this summary, the number and percentage of patients who report at least 1 TEAE in the ‘Nervous System Disorders’ SOC will also be summarized.

Outcomes will be evaluated by medical review to determine if a neurologic TEAE either preceded or occurred concurrently with any unexpected AEs of falls, fractures, sprains, head injury, etc., reported when the patients experienced the neurologic-related events. A listing will be provided for patients with adverse functional outcomes associated with neurologic events and includes the neurologic-related events and any other AEs identified through the medical review.

6.9.9.4. Drug Abuse Liability

The following event clusters will be used to evaluate potential abuse liability:

- The SMQ of Drug abuse and dependence [20000101], including individual PTs, all narrow terms and all (narrow and broad) terms.

- The LSC of “Additional potential abuse liability” terms. This LSC contains additional terms based on the Food and Drug Administration (FDA) guidance (FDA 2017) that are not included in the Drug abuse and dependence SMQ, including terms for Dissociation/psychotic, Euphoria, Impaired attention, cognition and mood and Other abuse-related terms. The term list is based on the latest version of MedDRA ([Appendix 4](#)).

The following will be summarized by treated migraine attacks and by patient for the evaluable population:

- For patients **CC** years of age, TEAEs within the SMQ and overall (any TEAE within the SMQ and/or LSC) sorted by decreasing frequency in PTs in the lasmiditan 200 mg group. For the SMQ, a summary and analysis by broad and narrow PTs will also be provided.
- For patients 6 to **CC** years of age, TEAEs within the SMQ sorted by decreasing frequency in PTs in the lasmiditan 200 mg group. A summary and analysis by broad and narrow PTs will also be provided.

The following additional summaries will be performed for patients **CC** years of age for the evaluable population:

- Time to onset and duration of key individual abuse liability (AL) TEAEs will be summarized, analyzed, and plotted. Abuse liability TEAEs are defined to be within either the SMQ or LSC.
- For patients with at least 2 key AL TEAEs, the onset times relative to the dose and the durations will be plotted by individual AL TEAEs.

The key AL terms include the following TEAEs:

- feeling abnormal
- euphoric mood
- feeling drunk
- abnormal dreams
- mental impairment
- dysphoria
- apathy
- hallucination
- hallucination, visual
- hallucination, auditory
- depersonalization/derealization disorder
- illusion

In addition to these analyses, a listing of patients in the enrolled population who reported overdose AEs will be provided. Overdose AEs consist of the following PTs:

- accidental overdose
- antemortem blood drug level abnormal

- antemortem blood drug level increased
- drug level above therapeutic
- drug level increased
- extra dose administered
- intentional overdose
- overdose
- postmortem blood drug level abnormal
- postmortem blood drug level increased
- prescribed overdose.

6.9.9.5. Suicide-Related Thoughts and Behaviors

6.9.9.5.1. *Columbia-Suicide Severity Rating Scale (C-SSRS)-Children's Version*

The C-SSRS will be administered at Screening (Visit 1), CCI [REDACTED], and Month 12 (Visit 7).

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring postbaseline, based on the C-SSRS, will be summarized by visit for the evaluable population. In addition, the number and proportion of patients who experienced at least 1 of various composite measures will be presented. These include:

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

Although not suicide-related, patients with non-suicidal self-injurious behavior (self-injurious behavior without suicidal intent and self-injurious behavior, intent unknown) occurring postbaseline will also be summarized.

Specifically, the following outcomes are C-SSRS categories and have binary responses (yes/no). The categories have been re-ordered from the actual scale to facilitate the definitions of the composite endpoints and to enable clarity in the presentation of the results.

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act

- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan
- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

Suicidal ideation, suicidal behaviour, and self-injurious behaviour without suicidal intent, based on the C-SSRS, will be listed for individual patients by visit. Only patients that show suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent will be displayed (i.e., if a patient's answers are all 'no' for the C-SSRS, then that patient will not be displayed). However, if a patient reported any suicidal ideation/behavior or self-injurious behavior without suicidal intent at any time point then all their C-SSRS responses, affirmative or negative, for all assessments will be displayed.

6.9.9.5.2. Self-Harm Follow-up Supplement Form

As part of the C-SSRS, the self-harm supplement follow-up form is administered for each event where the patient reports 1 or more self-harm events and provides more detail of the events. Responses to this form will be listed for each patient who reports 1 or more self-harm event.

6.9.9.5.3. Standardized MedDRA Query (SMQ)

In addition to the analyses of the C-SSRS results, treated migraine attacks and patients with PTs within the Suicide/Self Injury SMQ (20000037) will be summarized by decreasing frequency in the lasmiditan 200 mg group for the evaluable population.

6.9.9.6. Potential Hypersensitivity Events

Treated migraine attacks and patients with potential immediate hypersensitivity reactions (including anaphylaxis) will be summarized using the MedDRA PTs contained in any of the following SMQs for TEAEs and sorted by decreasing frequency in PTs in the lasmiditan 200 mg group for the evaluable population:

- Anaphylactic reaction SMQ (20000021; narrow and broad)
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad)

Treated migraine attacks and patients with potential non-immediate hypersensitivity reactions will be summarized using the MedDRA PTs contained in any of the following SMQs for AEs occurring after 48 hours of dosing and sorted by decreasing frequency in PTs in the lasmiditan 200 mg group for the evaluable population:

- Anaphylactic reaction SMQ (20000021; narrow and broad)
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad)

6.9.9.7. Motor Vehicle Accidents and Violations

Data from assessments of involvement in motor vehicle accidents or violations since last visit will be listed for patients who have at least 1 motor vehicle accident or violation.

6.10. Efficacy, Medical Resource Utilization, and Health Economics Analyses

All efficacy, medical resource utilization, and health economics analyses will be performed on the evaluable population. Efficacy assessments will be collected via CCI [REDACTED]. Medical resource utilization and health economics assessments will be collected via the CRF.

Table LAHW.6.5 includes the description, derivation and definition of missingness of the efficacy, medical resource utilization, and health economics measures and endpoints.

Table LAHW.6.6 includes the description of the analysis method, population and time point(s) of analysis for efficacy, medical resource utilization, and health economics measures. Assessments collected at multiple time points will be analyzed at each time point.

Table LAHW.6.5. Description and Derivation of Efficacy, Medical Resource Utilization, and Health Economics Measures and Endpoints

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
Migraine Pain Severity	Migraine pain severity will be recorded in the CCI using a 5-Face Pain Scale at each assessment time point (at the time of treatment with lasmiditan [baseline]; and 2-hours, 24-hours, and 48-hours after taking lasmiditan [postdose]). 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 (Maunuksele et al. 1987). The patient selects the number corresponding to the face that represents their current pain severity.	Proportion of treated mild, moderate, and severe migraine attacks with pain freedom 2-hours postdose Proportion of treated moderate and severe migraine attacks with pain freedom 2-hours postdose For treated mild, moderate, and severe migraine attacks: • Pain freedom 25 flag • Pain freedom 50 flag • Pain freedom 75 flag Proportion of treated mild, moderate, and severe migraine attacks with pain relief 2-hours	Number of treated migraine attacks with a reduction in baseline pain as measured on a 5-Face Pain Scale from mild (Face 2), moderate (Faces 3 and 4) or severe (Face 5) to no pain (Face 1) 2-hours postdose Number of treated migraine attacks with a reduction in baseline pain as measured on a 5-Face Pain Scale from moderate (Faces 3 and 4) or severe (Face 5) to no pain (Face 1) 2-hours postdose Number of patients with a proportion of treated mild, moderate, and severe migraine attacks with pain freedom 2-hours postdose >25%, 50%, or 75% Number of treated migraine attacks with a reduction in baseline pain from either:	Missing if assessment is missing at either baseline or 2-hours postdose Missing if assessment is missing at either baseline or 2-hours postdose Missing if assessment is missing at either baseline or 2-hours postdose Missing if assessment is missing at either baseline or 2-hours postdose

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		postdose	• moderate (Faces 3 and 4) or severe (Face 5) to mild or no pain (Face 1 or 2) 2-hours postdose; or • mild (Face 2) to no pain (Face 1) 2-hours postdose; or • patient is asleep 2-hours postdose	hours postdose
		For treated mild, moderate, and severe migraine attacks: • Pain relief 25 flag • Pain relief 50 flag • Pain relief 75 flag	Number of patients with a proportion of treated mild, moderate, and severe migraine attacks with pain relief 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated mild, moderate, or severe migraine attacks with sustained pain freedom 24-hours postdose	Number of treated migraine attacks with a reduction in baseline pain as measured on a 5-Face Pain Scale from: • Mild (Face 2), moderate (Faces 3 and 4) or severe (Face 5) to no pain (Face 1) at 2-hours and 24-hours postdose • and without the use of additional migraine medication for rescue on or	Missing if assessment is missing at baseline, 2-hours, or 24-hours postdose

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
			before 24-hours postdose.	
		For treated mild, moderate, and severe migraine attacks: • 24-hours sustained pain freedom 25 flag • 24-hours sustained pain freedom 50 flag • 24-hours sustained pain freedom 75 flag	Number of patients with a proportion of treated mild, moderate, and severe migraine attacks with sustained pain freedom 24-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at baseline, 2-hours, or 24-hours postdose For patients who reduced their dose, missing for treated migraine attacks at the reduced dose
		Proportion of treated mild, moderate, or severe migraine attacks with sustained pain freedom 48-hours postdose	Number of treated migraine attacks with a reduction in baseline pain as measured on a 5-Face Pain Scale from: • Mild (Face 2), moderate (Faces 3 and 4) or severe (Face 5) to no pain (Face 1) at 2-hours, 24-hours, and 48-hours postdose • and without the use of additional migraine medication for rescue on or before 48-hours postdose.	Missing if assessment is missing at baseline, 2-hours, 24-hours, or 48-hours postdose

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		For treated mild, moderate, and severe migraine attacks: • 48-hours sustained pain freedom 25 flag • 48-hours sustained pain freedom 50 flag • 48-hours sustained pain freedom 75 flag	Number of patients with a proportion of treated mild, moderate, and severe migraine attacks with sustained pain freedom 48-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at baseline, 2-hours, or 48-hours postdose
Meaningful Pain Relief	Patients will record, in their CCI, the time of when they began to feel better for each treated migraine attack.	Time to meaningful pain relief (hours) for the first treated migraine attack	For the patient's first treated migraine attack, date and time of when the patient reported they "begin to feel better" minus date and time of the reported administration of lasmiditan	Missing if date and time is missing
Associated Symptoms of Migraine: Most Bothersome Symptom (MBS)	The associated symptoms (yes/no) of migraine will be captured in the CCI at each assessment time point (at the time of treatment with lasmiditan [baseline] and 2-hours after taking lasmiditan [postdose]). The associated symptoms are the following: • Nausea • Phonophobia • Photophobia The patient is then asked to identify which symptom is the most bothersome. If a patient is experiencing 1 of the 3 associated symptoms at	Proportion of treated migraine attacks with resolution of the MBS 2-hours postdose	Of all treated migraine attacks with a defined MBS at baseline, number of attacks with an absence of that MBS 2-hours postdose.	Missing if assessment is missing at either baseline or 2-hours postdose
		• MBS resolution 25 flag • MBS resolution 50	Number of patients with a proportion of treated migraine attacks with	Missing if assessment is missing at either

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
Associated Symptoms of Migraine: Individual Symptoms	baseline, it will be defined as the MBS regardless of if the patient indicated it was the MBS.	flag MBS resolution 75 flag	resolution of the MBS 2-hours postdose >25%, 50%, or 75%	baseline or 2-hours postdose
	The associated symptoms (yes/no) of migraine will be captured in the CCI at each assessment time point (at the time of treatment with lasmiditan [baseline] and 2-hours after taking lasmiditan [postdose]). The associated symptoms are the following: - Nausea - Phonophobia - Photophobia	Proportion of treated migraine attacks nausea-free 2-hours postdose	Number of attacks with the absence of nausea 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose
		- Nausea-free 25 flag - Nausea-free 50 flag - Nausea-free 75 flag	Number of patients with a proportion of treated migraine attacks with the absence of nausea 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks with the resolution of nausea 2-hours postdose	Of all treated migraine attacks where the patient reported nausea as an associated symptom at baseline, number of attacks with resolution of nausea 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose
		- Nausea resolution 25 flag - Nausea resolution 50 flag - Nausea resolution 75 flag	Number of patients with a proportion of treated migraine attacks with resolution of nausea 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks phonophobia-free 2-hours postdose	Number of attacks with the absence of phonophobia 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		- Phonophobia-free 25 flag - Phonophobia-free 50 flag - Phonophobia-free 75 flag	Number of patients with a proportion of treated migraine attacks with the absence of phonophobia 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks with resolution of phonophobia 2-hours postdose	Of all treated migraine attacks where the patient reported phonophobia as an associated symptom at baseline, number of attacks with resolution of phonophobia 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose.
		- Phonophobia resolution 25 flag - Phonophobia resolution 50 flag - Phonophobia resolution 75 flag	Number of patients with a proportion of treated migraine attacks with resolution of phonophobia 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks photophobia-free 2-hours postdose	Number of attacks with the absence of photophobia 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose
		- Photophobia-free 25 flag - Photophobia-free 50 flag - Photophobia-free 75 flag	Number of patients with a proportion of treated migraine attacks with the absence of photophobia 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks photophobia-free 2-hours postdose	Number of attacks with the absence of photophobia 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
Additional Migraine Treatment for Recuse	Use of additional treatment for migraine will be recorded by the patient in the CCI and captured in the concomitant medication CRF at each visit.	Proportion of treated migraine attacks with resolution of photophobia 2-hours postdose	Of all treated migraine attacks where the patient reported photophobia as an associated symptom at baseline, number of attacks with resolution of photophobia 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose
		• Photophobia resolution 25 flag • Photophobia-resolution 50 flag • Photophobia resolution 75 flag	Number of patients with a proportion of treated migraine attacks with resolution of photophobia 2-hours postdose >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks where the patient used additional migraine medication for rescue within 48-hours postdose	Number of treated migraine attacks where the patient reported a concomitant medication with an indication for use = “acute migraine treatment” and with a start date and time that is within 48 hours of the administering lasmiditan.	Missing start date/time and stop date/time will be imputed by following the rules in Appendix 1 . If after applying the imputation rules, the start date is still missing then the medication will be considered a migraine medication for rescue if the stop date is either also missing or is

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
				within 48 hours of administering lasmiditan
		- Additional migraine medication 25 flag - Additional migraine medication 50 flag - Additional migraine medication 75 flag	Number of patients with treated migraine attacks with additional migraine medication for rescue within 48-hours postdose >25%, 50%, or 75%	Missing start date/time and stop date/time will be imputed by following the rules in Appendix 1 . If after applying the imputation rules, the start date is still missing then the medication will be considered a migraine medication for rescue if the stop date is either also missing or is within 48 hours of administering lasmiditan
		Time to use of additional migraine medication (hours) for the first treated migraine attack where the patient used additional migraine medication for rescue	For the first treated migraine attack where the patient used additional migraine medication for rescue, date and time of the first (in chronological time) reported	Missing start date/time will be imputed by following the rules in Appendix 1 . If after applying the

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
Interference in Daily Activities	A single CCI item 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 point (at the time of treatment with lasmiditan and 2-hours after taking lasmiditan): 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.		concomitant medication with an indication for use = “acute migraine treatment” minus the date and time of administration of lasmiditan for the corresponding migraine attack	imputation rules, the start date/time is still missing then the medication start time will be the time of administering lasmiditan
		Shift from baseline to 2-hours postdose in interference of daily activities rating for treated migraine attacks	Categories are: 0 (not at all) to: 0 (not at all) 1 (a little) 2 (a lot) 3 (completely) 1 (a little) to: 0 (not at all) 1 (a little) 2 (a lot) 3 (completely) 2 (a lot) to: 0 (not at all) 1 (a little) 2 (a lot) 3 (completely) 3 (completely) to: 0 (not at all) 1 (a little) 2 (a lot) 3 (completely)	Missing if assessment is missing at either baseline or 2-hours postdose
		Proportion of treated migraine attacks with a 2-hours postdose	Number of attacks reporting a rating of 0 (not at all) 2-hours	Missing if assessment is missing at either

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		interference in daily activities rating of 0 (not at all)	postdose	baseline or 2-hours postdose
		• Rating (0) 25 flag • Rating (0) 50 flag • Rating (0) 75 flag	Number of patients with a proportion of treated migraine attacks with a 2-hours postdose interference in daily activities rating of 0 (not at all) >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose For patients who reduced their dose, missing for treated migraine attacks at the reduced dose
		Proportion of treated migraine attacks with a 2-hours postdose interference in daily activities rating of 0 (not at all) or 1 (a little)	Number of patients reporting a rating of 0 (not at all) or 1 (a little) 2-hours postdose	Missing if assessment is missing at either baseline or 2-hours postdose
		• Rating (0,1) 25 flag • Rating (0,1) 50 flag • Rating (0,1) 75 flag	Number of patients with a proportion of treated migraine attacks with a 2-hours postdose interference in daily activities rating of 0 (not at all) or 1 (a little) >25%	Missing if assessment is missing at either baseline or 2-hours postdose For patients who reduced their dose, missing for treated migraine attacks at the reduced dose
		Proportion of treated	Number of patients	Missing if

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
Pediatric Migraine Disability Assessment Scale (PedMIDAS)	The PedMIDAS captures disability due to migraine at screening, Month CCI 12, and early discontinuation in the CRF. 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. The instrument consists of 6 items, in which the number of disabled days due to headache over the past 3 months are captured, including: 1. full days missed from school 2. partial days missed from school 3. functionally impaired days in school 4. functionally impaired days at home 5. inability to participate in extracurricular	migraine attacks with a 2-hour postdose interference in daily activities rating of 0 (not at all), 1 (a little), or 2 (a lot)	reporting a rating of 0 (not at all), 1 (a little), or 2 (a lot) 2-hours postdose	assessment is missing at either baseline or 2-hours postdose
		• Rating (0,1,2) 25 flag • Rating (0,1,2) 50 flag • Rating (0,1,2) 75 flag	Number of patients with a proportion of treated migraine attacks with a 2-hours postdose interference in daily activities rating of 0 (not at all), 1 (a little), or 2 (a lot) >25%, 50%, or 75%	Missing if assessment is missing at either baseline or 2-hours postdose For patients who reduced their dose, missing for treated migraine attacks at the reduced dose
		• PedMIDAS total score • Change from baseline in PedMIDAS total score	Sum of the number of reported disabled days from the 6 items, range is 0-540. Higher values are indicative of a greater level of disability due to headache	Missing if assessment is missing
		• Total number of days with a headache, in the last 3 months • Change from baseline in the total number of days with a headache, in the	Number of days with a headache	Missing if assessment is missing

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	and leisure activities, and functionally impaired days of extracurricular and leisure activities. 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, two 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)	last 3 months	Score associated with the average pain experienced with headaches in the last 3 months, range is 0-10. Higher values are indicative of the greater level of pain	Missing if assessment is missing
		- Headache pain - Change from baseline in headache pain		
Pediatric Quality of Life Inventory™ (PedsQL)	The PedsQL 4.0 Generic Core Scales are a general health measure designed to specifically evaluate quality of life and functioning in children and adolescents. The instrument has age-specific questionnaires (based on the age at Visit 1) to ensure the validity and reliability within developmentally-appropriate groups; hence there are specific forms for those in the following age ranges (Varni et al. 2001, 2002; Powers et al. 2003; Schwimmer et al. 2003): 5 to 7 years (Young Child), 8 to 12 years (Child), and 13 to 18 years (Teen). The paper questionnaires consist of 23 items measuring the level of impairment over the past month and are administered at screening, Month CCI, 12, and early discontinuation. Responses	- PedsQL item scores - Change from baseline in PedsQL item scores	Item scores are reverse transformed to a 0-100 scale as follows: 0=100 1=75 2=50 3=25 4=0 Higher scores indicate better health-related quality of life	Missing if assessment is missing
		- Total Score - Change from baseline in total score	Mean of all non-missing item scores (23 items); range 0-100; higher scores indicate better health-related quality of life	

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	are then transcribed to the CRF. A 3-point response scale (0=Not at all, 2=Sometimes, 4=A lot) is used for the Young Child questionnaire were a 5-point response scale (0=Never, 1=Almost never, 2=Sometimes, 3=Often, 4=Almost always) is used for the Child and Teen questionnaires. The instrument is considered sensitive and appropriate for use in acute or chronic illnesses (Varni et al. 2001, 2002).	- Physical health summary / Physical functioning domain score - Change from baseline in physical health summary / physical functioning domain score	The physical health summary score is equal to the physical functioning domain score: Mean of the non-missing physical functioning item scores (8 items); range 0-100; higher scores indicate better physical functioning/health	If more than 50% of the items in the score is missing, then missing
		- Emotional functioning domain score - Change from baseline in emotional functioning domain score	Mean of the non-missing emotional functioning item scores (5 items); range 0-100; higher scores indicate better emotional functioning	If more than 50% of the items in the score is missing, then missing
			Emotional functioning domain score minus emotional functioning domain score at screening	If more than 50% of the items in the score is missing, then missing. If missing at screening, then missing
		- Social functioning domain score - Change from baseline in social functioning domain score	Mean of the non-missing social functioning item scores (5 items); range 0-100; higher scores indicate better social functioning	If more than 50% of the items in the score is missing, then missing
		School functioning domain score	Mean of the non-missing school functioning item	If more than 50% of the items in

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
Health Care Resource Utilization	Health care resource utilization associated with medical encounters will be collected in the CRF at screening (baseline), Month CCI, 12, and early discontinuation. Protocol mandated procedures, tests, and encounters are excluded. The data collected will include: - number of hospital emergency room visits and visits related to a migraine, - number and duration (total days) of hospital overnight visits and visits related to a migraine, and - number of other healthcare professional visits (physician of any specialty, nurse, rehabilitation specialist, physical therapist, psychologist or counselor, urgent care center, etc.) and visits related to a migraine. Data collected at screening refers to the past 6 months, whereas, data collected at Month CCI 12, and early discontinuation refers to the last study visit.	Change from baseline in school functioning domain score	scores (5 items); range 0-100; higher scores indicate better school functioning	the score is missing, then missing
		- Psychosocial health summary score - Change from baseline in psychosocial health summary score	Mean of the non-missing emotional, social, and school function item scores (15 items). Range 0-100; higher scores indicate better psychosocial health	If more than 50% of the items in the score is missing, then missing
		Proportion of patients with at least 1: - emergency room visit - emergency room visit related to migraine	Number of patients with at least 1: - emergency room visit - emergency room visit related to migraine	Missing if assessment is missing
		Number of: - emergency room visits - emergency room visits related to migraine	Of the patients reporting at least 1 emergency room visit, total number of reported: - emergency room visits - emergency room visits related to migraine	Missing if assessment is missing
		Proportion of patients with at least 1: - hospital overnight visit - hospital overnight	Number of patients with at least 1: - hospital overnight visit - hospital overnight	Missing if assessment is missing

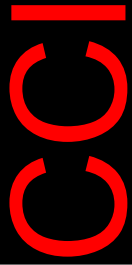
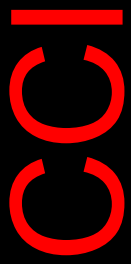
Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	In addition to the health care resource utilization questions, the following question is included “During the last 3 months, how many weeks was school in session?”	visits related to migraine	visit related to migraine	
		Number of: • hospital overnight visits • hospital overnight visits related to migraine	Of the patients reporting at least 1 hospital overnight stay, total number of: • hospital overnight visits • hospital overnight visits related to migraine	Missing if assessment is missing
		Duration (days) of: • hospital overnight visits • hospital overnight visits related to migraine	Of the patients reporting at least 1 hospital overnight stay, duration in days of: • hospital overnight visits • hospital overnight visits related to migraine	Missing if assessment is missing
		Proportion of patients with at least 1: • healthcare professional visit • healthcare professional visit related to migraine	Number of patients reporting at least 1: • healthcare professional visit • healthcare professional visit related to migraine	Missing if assessment is missing
		Number of: • healthcare professional visits • healthcare professional visits	Of the patients reporting at least 1 healthcare profession visit, total number: • healthcare	Missing if assessment is missing

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		related to migraine	professional visits • healthcare professional visits related to migraine	
		Number of weeks school was in session	Number of reported weeks that school was in session	Missing if assessment is missing

Table LAHW.6.6. Description of Efficacy, Medical Resource Utilization, and Health Economics Analysis

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
Migraine Pain Severity	Proportion of treated mild, moderate, or severe migraine attacks with pain freedom 2-hours postdose	Evaluable Population – number of treated mild, moderate, or severe migraine attacks at baseline	Descriptive statistics (observed and NRI)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Primary and Supportive
	Proportion of treated moderate or severe migraine attacks with pain freedom 2-hours postdose	Evaluable Population – number of treated moderate or severe migraine attacks at baseline	Descriptive statistics (observed and NRI)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary and Supportive
	For treated mild, moderate and severe migraine attacks:	Evaluable Population	Descriptive statistics (observed and NRI)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	• Pain freedom 25 flag					
	• Pain freedom 50 flag					
	• Pain freedom 75 flag					
	Proportion of treated mild, moderate, or severe migraine attacks with pain relief 2-hours	Evaluable Population – number of treated mild, moderate, or severe migraine attacks at	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	postdose	baseline				
	For treated mild, moderate, and severe migraine attacks: - Pain relief 25 flag - Pain relief 50 flag - Pain relief 75 flag	Evaluate Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated mild, moderate, or severe migraine attacks with sustained pain freedom 24-hours postdose	Evaluate Population – number of treated mild, moderate, or severe migraine attacks at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	For treated mild, moderate, and severe migraine attacks: 24-hours sustained pain freedom 25 flag 24-hours sustained pain freedom 50 flag 24-hours sustained pain freedom 75 flag	Evaluate Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated	Evaluate	Descriptive	0 to 3 months	LTN 100mg	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	mild, moderate, or severe migraine attacks with sustained pain freedom 48-hours postdose	Population – number of treated mild, moderate, or severe migraine attacks at baseline	statistics (observed)	>3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 200mg 	
	For treated mild, moderate, and severe migraine attacks: 48-hours sustained pain freedom 25 flag 48-hours sustained pain freedom 50 flag 48-hours sustained pain freedom 75 flag	Evaluate Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
Meaningful Pain Relief	Time to meaningful pain relief (hours) for the first treated migraine attack	Evaluate Population	Descriptive Statistics (including Kaplan Meier estimates of the survival curve)	0 to 48 hours	LTN 100mg LTN 200mg	Secondary
Associated Symptoms of Migraine: Most Bothersome Symptom	Proportion of treated migraine attacks with resolution of the most bothersome symptom (MBS) 2-hours postdose	Evaluate Population – number of treated migraine attacks with least 1 associated symptom of migraine at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg 	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	- MBS resolution 25 flag - MBS resolution 50 flag - MBS resolution 75 flag	Evaluable Population – patients who report at least 1 migraine attack with at least 1 associated symptom of migraine at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
Associated Symptoms of Migraine: Individual Symptoms	Proportion of treated migraine attacks nausea-free 2-hours postdose	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg CCI	Secondary
	- Nausea-free 25 flag - Nausea-free 50 flag - Nausea-free 75 flag	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks with resolution of nausea 2-hours postdose	Evaluable Population – number of treated migraine attacks with nausea at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg CCI	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	- Nausea resolution 25 flag - Nausea resolution 50 flag - Nausea resolution 75 flag	Evaluable Population – patients who report at least 1 migraine attack with nausea at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks phonophobia-free 2-hours postdose	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg CCI	Secondary
	- Phonophobia-free 25 flag - Phonophobia-free 50 flag - Phonophobia-free 75 flag	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks with resolution of phonophobia 2-hours postdose	Evaluable Population – number of treated migraine attacks with phonophobia at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg CCI	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	- Phonophobia resolution 25 flag - Phonophobia resolution 50 flag - Phonophobia resolution 75 flag	Evaluable Population – patients who report at least 1 migraine attack with phonophobia at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks photophobia-free 2-hours postdose	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg CCI	Secondary
	- Photophobia-free 25 flag - Photophobia-free 50 flag - Photophobia-free 75 flag	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks with resolution of photophobia 2-hours postdose	Evaluable Population – number of treated migraine attacks with photophobia at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg CCI	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	- Photophobia resolution 25 flag - Photophobia resolution 50 flag - Photophobia resolution 75 flag	Evaluable Population – patients who report at least 1 migraine attack with photophobia at baseline	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
Additional Migraine Treatment for Rescue	Proportion of treated migraine attacks where the patient used additional migraine medication for rescue within 48-hours postdose	Evaluable Population – number of treated migraine attacks	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	- Additional migraine medication 25 flag - Additional migraine medication 50 flag - Additional migraine medication 75 flag	Evaluable Population – patients who report at least 1 migraine attack with the use of additional migraine medication for rescue	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	Time to use of additional migraine medication (hours) for the first treated migraine attack where the patient used additional migraine medication for rescue	Evaluable Population – patients who report at least 1 migraine attack with the use of additional migraine medication for rescue	Descriptive Statistics (including Kaplan Meier estimates of the survival curve)	0 to 48 hours	LTN 100mg LTN 200mg	Secondary
Interference in Daily Activities	Shift from baseline to 2-hours postdose in interference of daily activities rating for treated migraine attacks	Evaluable Population – number of treated migraine attacks	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks with a 2-hours postdose interference in daily activities rating of 0 (not at all)	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	- Rating (0) 25 flag - Rating (0) 50 flag - Rating (0) 75 flag	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	Proportion of treated migraine attacks	Evaluable Population	Descriptive statistics	0 to 3 months >3 to 6 months	LTN 100mg LTN 200mg	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
	with a 2-hours postdose interference in daily activities rating of 0 (not at all) or 1 (a little)		(observed)	>6 to 9 months >9 to 12 months 0 to 12 months	CCI	CCI
	• Rating (0,1) 25 flag • Rating (0,1) 50 flag • Rating (0,1) 75 flag	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months		
	Proportion of treated migraine attacks with a 2-hours postdose interference in daily activities rating of 0 (not at all), 1 (a little), or 2 (a lot)	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
	• Rating (0,1,2) 25 flag • Rating (0,1,2) 50 flag • Rating (0,1,2) 75 flag	Evaluable Population	Descriptive statistics (observed)	0 to 3 months >3 to 6 months >6 to 9 months >9 to 12 months 0 to 12 months	LTN 100mg LTN 200mg	Secondary
					CCI	CCI
					LTN 100mg LTN 200mg	Secondary

CCI

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
CCI						

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
CCI						

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
[REDACTED]						

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Assessment Time Points	Treatment Groups (Section 6.1)	Analysis Type
CCI						

Abbreviations: LR = last received; LTN = lasmiditan; mg = milligrams; NRI = nonresponder imputation; PBO = placebo.

6.10.1. Methodology for Secondary and Exploratory Analyses

All summaries for the lasmiditan 50 mg treatment group will be exploratory due to expected limitations in sample size.

6.10.1.1. Analyses by Treated Migraine Attack

All efficacy analyses summarized by treated migraine attack performed for the evaluable population.

Categorical summaries will include sample size (total number of treated migraine attacks), frequency counts, proportions, and 95% CIs for the proportion. Summaries will be conducted for the following timepoints:

- quarterly: 0 to 3 months, >3 to 6 months, >6 to 9 months, >9 to 12 months
- 0 to 12 months

Summaries will be conducted using observed data where the data is censored following the administration of additional migraine medication for rescue. A supportive summary for pain freedom at 2-hours postdose will be conducted using a NRI where patients are classified as nonresponders if their data is missing or following the administration of additional migraine medication for rescue. For patients who are asleep at any given timepoint after dosing, outcomes will be assumed to have achieved pain relief. See Section 6.4 for additional details.

6.10.1.2. Analyses by Patient

All efficacy analyses summarized by patient will be performed for the evaluable population.

Categorical summaries will include sample size (total number of patients), frequency counts, proportions, and 95% CIs for the proportion. Summaries will be conducted for the following timepoints:

- quarterly: 0 to 3 months, >3 to 6 months, >6 to 9 months, >9 to 12 months
- 0 to 12 months

Summaries will be conducted using observed data where the data is censored following the administration of additional migraine medication for rescue. A supportive summary for pain freedom at 2-hours postdose will be conducted using a NRI where patients are classified as nonresponders if their data is missing or following the administration of additional migraine medication for rescue. For patients who are asleep at any given timepoint after dosing, outcomes will be assumed to have achieved pain relief. See Section 6.4 for additional details.

Additionally, a supportive summary for pain freedom at 2-hours postdose will be conducted where data after a patient reduces their dose will be censored.

6.10.1.3. Analyses by Visit

All medical resource utilization and health economics analyses summarized by visit will be performed for the evaluable population.

Categorical data will include sample size (total number of patients), frequency counts, proportions, and 95% CIs for the proportion. Continuous data will include the sample size (total number of patients), mean, SD, minimum, median, and maximum. Change from baseline will be calculated as the postbaseline value minus the baseline value. Change from baseline analyses will include patients who have a baseline and a postbaseline assessment.

Summaries will be conducted for observed data by visit: CCI [REDACTED], and Month 12 (Visit 7).

6.10.1.4. Kaplan Meier Analyses

Efficacy analyses for time to event endpoints will be estimated for the first treated migraine attack using Kaplan-Meier curves by lasmiditan dose (lasmiditan 100 mg and lasmiditan 200 mg) for the evaluable population. Patients who not experience the event of interest will be censored 48 hours after dosing with lasmiditan. The Kaplan-Meier estimates and 95% CIs for the time that 25%, 50%, and 75% of patients experienced the event of interest will be presented. The number of patients experiencing the event of interest and the number of patients censored will be included.

6.11. Protocol Deviations

Important protocol deviations are defined as follows:

- Not meeting all inclusion or exclusion criteria
- Not obtaining informed consent or ascent
- Not reporting a SAE appropriately (i.e., within 24 hours)
- Discontinuation criteria met but did not discontinue
- Missing laboratory result/s
- Missing urine or serum pregnancy test
- CCI [REDACTED]
- Site over or under dosed patient (provided wrong blister pack CCI [REDACTED])
- Improper destruction/return of study medication
- Study medication lost or stolen
- Patient took study medication, but documentation of treated migraine is missing from their CCI [REDACTED]
- C-SSRS administered inappropriately

Protocol deviations will be listed for the enrolled population.

6.12. Subgroup Analyses

Subgroup analyses for all safety and efficacy endpoints will be conducted for age groups (6 to >CCI [REDACTED] years of age, ≥CCI [REDACTED] years of age) and analyses will be conducted similarly to those described in Sections 6.9 and 6.10.

For the subgroup analyses, age will be calculated using the difference in days between the date of birth and the date of informed consent. For sites that prohibit date of birth collection by privacy law, age will be imputed as follows:

- If month and year are reported, age will be the difference in days between the first day of the month and year of birth and the date of informed consent.
- If only year is reported, age will be the difference in days between July 1st of the year of birth and the date of informed consent.

6.13. Interim Analyses and Data Monitoring

A data monitoring committee (DMC) consisting of members external to Lilly will be established for safety monitoring of Study LAHV and Study LAHW. This committee will consist of a minimum of 3 members including a physician with an expertise in pediatrics and a statistician. No member of the DMC may have contact with study sites.

The first DMC analysis for safety may be performed 6 months after FPV occurs for Study LAHV. Additional DMC analyses for safety may be performed twice a year until Study LAHW has reached database lock. In addition to these planned data review meetings, the DMC will have the ability to hold ad hoc meetings, should they be deemed necessary.

The purpose of the external DMC is to monitor safety. The DMC may recommend stopping the study for safety, modifying the study for safety, or continuing the study with no modifications. The DMC may request efficacy data to put safety observations into context and to confirm a reasonable benefit/risk relation for ongoing patients in the study. The study may not be stopped for positive efficacy or futility. Hence, there will be no alpha adjustment for these interim analyses.

Details of the DMC analysis will be documented in the Lasmiditan Pediatric Phase 3 Program DMC charter and the interim analysis plan for studies LAHV and LAHW.

7. References

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Appendix 1. Imputation Rules for Missing Medication and Adverse Event Start Date/Time and Stop Date/Time

Imputed dates/times will not be included in listings.

Missing medication start date/time and stop date/time will be imputed by the rules below:

Endpoint	Medication imputation rule, to follow in order
Start date	If year, month, and day are missing, then start date will not be imputed and will remain missing. If year is missing, then year will be imputed as the year of the screening visit. If month and day is missing, then impute as January 1st. If month is missing and day is non-missing, then month will be imputed as January. If day is missing and month is non-missing, then day will be imputed as 1 for the first day of the month. If imputed start date is after the stop date, then start date will be imputed as the stop date.
Start time	If hour is missing: • If start date is equal to the study drug dose date, then time will be imputed as the time of the study drug dose. • Otherwise, time will be imputed as "00:00:00". If hour is non-missing and minutes and/or seconds are missing: • If start date and hour is equal to the study drug dose date and hour, then time will be imputed as the time of the study drug dose. • Otherwise, minutes and/or seconds will be imputed as "00".
Stop date	If year, month, and day are missing, then stop date will not be imputed and will remain missing. If year is missing, then year will be imputed as the year of the EOS or early discontinuation visit. If month and day is missing, then impute as December 31st. If month is missing and day is non-missing, then month will be

	imputed as December. If day is missing and month is non-missing, then day will be imputed as the last day of the month. If imputed stop date is before start date, then stop date will be imputed as start date.
Stop time	If hour is missing, then time will be imputed as "23:59:59". If only minutes and/or and seconds missing, then minutes and/or seconds will be imputed as "59".

Missing AE start date/time and stop date/time will be imputed by the rules below:

AE start date/time	AE stop date/time	AE imputation rule, to follow in order
non-missing	non-missing, partially missing, or missing	If AE start date/time < study drug dose date/time, then not considered a TEAE. If AE start date/time $\geq$ study drug dose date/time and < (study drug dose date/time + 48 hours [or 2 days]), then considered a TEAE.
partially missing, but known components show that it cannot be on or within 48 hours after study drug dose date/time	non-missing, partially missing, or missing	Not considered a TEAE.
partially missing, but known components show it could be on or within 48 hours after study drug dose date/time	non-missing	If AE stop date/time < study drug dose date/time, then not considered a TEAE. If AE stop date/time $\geq$ study drug dose date/time, then considered a TEAE.
	partially missing	Impute AE stop date/time as latest possible date/time (eg, last day of month if day missing or 31st December if day and month are missing), then: If AE stop date/time < study drug dose date/time, then not considered a TEAE. If AE stop date/time $\geq$ study drug dose date/time, then considered a TEAE.

AE start date/time	AE stop date/time	AE imputation rule, to follow in order
	missing	Considered a TEAE.
missing	non-missing	If AE stop date/time < study drug dose date/time, then not considered a TEAE. If AE stop date/time ≥ study drug dose date/time, then considered a TEAE.
	partially missing	Impute stop date/time as latest possible date/time (eg, last day of month if day unknown or 31st December if day and month are unknown), then: If AE stop date/time < study drug dose date/time, then not considered a TEAE. If AE stop date/time ≥ study drug dose date/time, then considered a TEAE.
	missing	Considered a TEAE.

Appendix 2. Possible Effects on Mental Ability

Possible Effects on Mental Ability

The following are the MedDRA v23.0 terms that represent possible effects on mental ability, based on FDA guidance for driving assessment, and medical judgment. The latest version of MedDRA will be used for the analysis.

Preferred Term (PT)	PT code
Change in sustained attention	10008398
Daydreaming	10057315
Distractibility	10013486
Executive dysfunction	10070246
Mental fatigue	10076757
Confusional state	10010305
Delirium	10012218
Disorientation	10013395
Bradyphrenia	10050012
Illogical thinking	10021402
Incoherent	10021630
Perseveration	10034703
Thinking abnormal	10043431
Impaired reasoning	10071176
Amnesia	10001949
Amnesic disorder	10061423
Borderline mental impairment	10052393
Cognitive disorder	10057668
Disturbance in attention	10013496
Judgement impaired	10023236
Memory impairment	10027175
Mental impairment	10027374
Retrograde amnesia	10038965
Transient global amnesia	10044380
Altered state of consciousness	10001854
Apraxia	10003062
Hemiapraxia	10048845
Visual agnosia	10077168
Visuospatial deficit	10080880
Trance	10044334
Mental status changes	10048294
Depressed level of consciousness	10012373
Loss of consciousness	10024855
Stupor	10042264

Syncope	10042772
Sudden onset of sleep	10050014
Somnolence	10041349
Hypersomnia	10020765
Lethargy	10024264
Vertigo	10047340
Dizziness postural	10013578
Dizziness	10013573
Sedation	10039897
Feeling drunk	10016330

Appendix 3. Cogstate Normative Population Standard Deviation and Test-Retest Reliability Values

For each Cogstate test, normative population standard deviation (s_{norm}) and test-retest reliability (r) values are listed below for each age (Cromer et al. 2015; Hammers et al. 2013; Mollica et al. 2005; Rosenfeld et al. 2018; Yoshida et al. 2011).

Detection Test (Reaction Time)

Age	s_{norm}	r
6	0.09264	0.79
7	0.09901	0.79
8	0.13746	0.79
9	0.13506	0.79
10	0.08007	0.79
11	0.07896	0.79
12	0.07682	0.79
13	0.07535	0.79
14	0.08101	0.79
15	0.07674	0.79
16	0.07644	0.79
17	0.07528	0.79

Identification Test (Reaction Time)

Age	s_{norm}	r
6	0.06801	0.80
7	0.07695	0.80
8	0.11548	0.80
9	0.09222	0.80
10	0.07096	0.80
11	0.07068	0.80
12	0.06719	0.80
13	0.06782	0.80
14	0.06954	0.80
15	0.06687	0.80
16	0.06561	0.80
17	0.06456	0.80

One Back Test (Reaction Time)

Age	s_{norm}	r
6	0.06515	0.78
7	0.11496	0.78
8	0.11140	0.78
9	0.11960	0.78
10	0.09147	0.78
11	0.08742	0.78
12	0.08970	0.78
13	0.08832	0.78
14	0.08875	0.78
15	0.08837	0.78
16	0.08920	0.78
17	0.09017	0.78

One Card Learning Test (Accuracy)

Age	s_{norm}	r
6	0.16830	0.70
7	0.17329	0.70
8	0.14007	0.70
9	0.16395	0.70
10	0.08819	0.70
11	0.08805	0.70
12	0.08754	0.70
13	0.08762	0.70
14	0.08567	0.70
15	0.08539	0.70
16	0.08588	0.70
17	0.08719	0.70

Appendix 4. Lilly Search Category of Additional Potential Abuse Liability Terms

Lilly Search Category (LSC) of Additional Potential Abuse Liability Terms

The following are the MedDRA v23.0 terms and categories to comprise the Lilly Search Category. The latest version of MedDRA will be used for the analysis of drug abuse potential.

LSC Terms	Preferred Term (PT)	PT code
Dissociation/psychotic	ACUTE PSYCHOSIS	10001022
Dissociation/psychotic	AGGRESSION	10001488
Dissociation/psychotic	AGITATION	10001497
Dissociation/psychotic	ALICE IN WONDERLAND SYNDROME	10001666
Dissociation/psychotic	ANGER	10002368
Dissociation/psychotic	ANTISOCIAL BEHAVIOUR	10002820
Dissociation/psychotic	BELLIGERENCE	10004224
Dissociation/psychotic	CONFABULATION	10010297
Dissociation/psychotic	CONFUSIONAL AROUSAL	10067494
Dissociation/psychotic	CONFUSIONAL STATE	10010305
Dissociation/psychotic	DEJA VU	10012177
Dissociation/psychotic	DELIRIUM	10012218
Dissociation/psychotic	DELUSION	10012239
Dissociation/psychotic	DELUSION OF GRANDEUR	10012241
Dissociation/psychotic	DELUSION OF REFERENCE	10012244
Dissociation/psychotic	DELUSION OF REPLACEMENT	10012245
Dissociation/psychotic	DELUSIONAL DISORDER, EROTOMANIC TYPE	10012249
Dissociation/psychotic	DELUSIONAL DISORDER, GRANDIOSE TYPE	10012250
Dissociation/psychotic	DELUSIONAL DISORDER, JEALOUS TYPE	10012251
Dissociation/psychotic	DELUSIONAL DISORDER, MIXED TYPE	10012252
Dissociation/psychotic	DELUSIONAL DISORDER, PERSECUTORY TYPE	10053195
Dissociation/psychotic	DELUSIONAL DISORDER, SOMATIC TYPE	10012254
Dissociation/psychotic	DELUSIONAL DISORDER, UNSPECIFIED TYPE	10012255
Dissociation/psychotic	DELUSIONAL PERCEPTION	10012258
Dissociation/psychotic	DEPERSONALISATION/DEREALISATION DISORDER	10077805
Dissociation/psychotic	DEPRESSIVE DELUSION	10063033
Dissociation/psychotic	DERAILMENT	10012411
Dissociation/psychotic	DIENCEPHALIC SYNDROME OF INFANCY	10012774
Dissociation/psychotic	DISORIENTATION	10013395
Dissociation/psychotic	DISSOCIATION	10013457
Dissociation/psychotic	DISSOCIATIVE AMNESIA	10013461
Dissociation/psychotic	DISSOCIATIVE IDENTITY DISORDER	10013468

Dissociation/psychotic	EROTOMANIC DELUSION	10015134
Dissociation/psychotic	FEAR	10016275
Dissociation/psychotic	FLASHBACK	10016754
Dissociation/psychotic	FORMICATION	10017062
Dissociation/psychotic	FRUSTRATION TOLERANCE DECREASED	10077753
Dissociation/psychotic	HALLUCINATION	10019063
Dissociation/psychotic	HALLUCINATION, AUDITORY	10019070
Dissociation/psychotic	HALLUCINATION, GUSTATORY	10019071
Dissociation/psychotic	HALLUCINATION, OLFACTORY	10019072
Dissociation/psychotic	HALLUCINATION, SYNAESTHETIC	10062824
Dissociation/psychotic	HALLUCINATION, TACTILE	10019074
Dissociation/psychotic	HALLUCINATION, VISUAL	10019075
Dissociation/psychotic	HALLUCINATIONS, MIXED	10019079
Dissociation/psychotic	HOMICIDAL IDEATION	10049666
Dissociation/psychotic	HOMICIDE	10020364
Dissociation/psychotic	HOSTILITY	10020400
Dissociation/psychotic	HYPERVIGILANCE	10048533
Dissociation/psychotic	HYPNAGOGIC HALLUCINATION	10020927
Dissociation/psychotic	HYPNOPOMPIC HALLUCINATION	10020928
Dissociation/psychotic	HYSTERICAL PSYCHOSIS	10062645
Dissociation/psychotic	IDEAS OF REFERENCE	10021212
Dissociation/psychotic	ILLOGICAL THINKING	10021402
Dissociation/psychotic	ILLUSION	10021403
Dissociation/psychotic	IMPATIENCE	10049976
Dissociation/psychotic	IRRITABILITY	10022998
Dissociation/psychotic	JAMAIS VU	10023118
Dissociation/psychotic	JEALOUS DELUSION	10023164
Dissociation/psychotic	MAGICAL THINKING	10025429
Dissociation/psychotic	MIXED DELUSION	10076429
Dissociation/psychotic	PANIC ATTACK	10033664
Dissociation/psychotic	PANIC REACTION	10033670
Dissociation/psychotic	PARAMNESIA	10033848
Dissociation/psychotic	PARANOIA	10033864
Dissociation/psychotic	PARASOMNIA	10061910
Dissociation/psychotic	PAROXYSMAL PERCEPTUAL ALTERATION	10063117
Dissociation/psychotic	PERSECUTORY DELUSION	10034702
Dissociation/psychotic	PERSONALITY CHANGE	10034719
Dissociation/psychotic	PERSONALITY DISORDER	10034721
Dissociation/psychotic	PHYSICAL ASSAULT	10034983
Dissociation/psychotic	PSYCHOTIC BEHAVIOUR	10037249
Dissociation/psychotic	PSYCHOTIC DISORDER	10061920
Dissociation/psychotic	REACTIVE PSYCHOSIS	10053632
Dissociation/psychotic	REBOUND PSYCHOSIS	10074833

Dissociation/psychotic	SENSORY DISTURBANCE	10040026
Dissociation/psychotic	SENSORY LEVEL ABNORMAL	10061567
Dissociation/psychotic	SLEEP SEX	10067492
Dissociation/psychotic	SLEEP TERROR	10041010
Dissociation/psychotic	SOMATIC DELUSION	10041317
Dissociation/psychotic	SOMATIC HALLUCINATION	10062684
Dissociation/psychotic	STARING	10041953
Dissociation/psychotic	SUSPICIOUSNESS	10042635
Dissociation/psychotic	THOUGHT BLOCKING	10043495
Dissociation/psychotic	THOUGHT BROADCASTING	10052214
Dissociation/psychotic	THOUGHT INSERTION	10043496
Dissociation/psychotic	THOUGHT WITHDRAWAL	10043497
Dissociation/psychotic	TRANSIENT PSYCHOSIS	10056326
Dissociation/psychotic	VIOLENCE-RELATED SYMPTOM	10047426
Euphoria	ABNORMAL BEHAVIOUR	10061422
Euphoria	ATTENTION-SEEKING BEHAVIOUR	10003739
Euphoria	CENTRAL NERVOUS SYSTEM STIMULATION	10061444
Euphoria	DISINHIBITION	10013142
Euphoria	DIZZINESS	10013573
Euphoria	ENERGY INCREASED	10048779
Euphoria	EUPHORIC MOOD	10015535
Euphoria	FEELING ABNORMAL	10016322
Euphoria	FEELING DRUNK	10016330
Euphoria	FEELING JITTERY	10016338
Euphoria	FEELING OF RELAXATION	10016352
Euphoria	FLIGHT OF IDEAS	10016777
Euphoria	GAMBLING DISORDER	10078070
Euphoria	HOT FLUSH	10060800
Euphoria	IMPULSIVE BEHAVIOUR	10021567
Euphoria	INAPPROPRIATE AFFECT	10021588
Euphoria	INCOHERENT	10021630
Euphoria	JUDGEMENT IMPAIRED	10023236
Euphoria	LOGORRHOEA	10024796
Euphoria	LOOSE ASSOCIATIONS	10024825
Euphoria	MANIA	10026749
Euphoria	MOOD SWINGS	10027951
Euphoria	PSYCHOMOTOR HYPERACTIVITY	10037211
Euphoria	RESTLESSNESS	10038743
Euphoria	TANGENTIALITY	10043114
Euphoria	THINKING ABNORMAL	10043431
Impaired attention, cognition and mood	ABNORMAL DREAMS	10000125
Impaired attention, cognition and mood	ABNORMAL SLEEP-RELATED EVENT	10061613
Impaired attention, cognition and mood	AFFECT LABILITY	10054196

Impaired attention, cognition and mood	AFFECTIVE DISORDER	10001443
Impaired attention, cognition and mood	ALEXITHYMIA	10077719
Impaired attention, cognition and mood	ALTERED STATE OF CONSCIOUSNESS	10001854
Impaired attention, cognition and mood	ALTERED VISUAL DEPTH PERCEPTION	10053549
Impaired attention, cognition and mood	AMNESIA	10001949
Impaired attention, cognition and mood	AMNESTIC DISORDER	10061423
Impaired attention, cognition and mood	ANHEDONIA	10002511
Impaired attention, cognition and mood	ANTEROGRADE AMNESIA	10002711
Impaired attention, cognition and mood	ANXIETY	10002855
Impaired attention, cognition and mood	APATHY	10002942
Impaired attention, cognition and mood	ASOCIAL BEHAVIOUR	10003472
Impaired attention, cognition and mood	ASTHENIA	10003549
Impaired attention, cognition and mood	BALANCE DISORDER	10049848
Impaired attention, cognition and mood	BLUNTED AFFECT	10005885
Impaired attention, cognition and mood	BRADYPHRENIA	10050012
Impaired attention, cognition and mood	COGNITIVE DISORDER	10057668
Impaired attention, cognition and mood	COMPULSIONS	10010219
Impaired attention, cognition and mood	CONSCIOUSNESS FLUCTUATING	10050093
Impaired attention, cognition and mood	COORDINATION ABNORMAL	10010947
Impaired attention, cognition and mood	CRYING	10011469
Impaired attention, cognition and mood	DEPRESSED LEVEL OF CONSCIOUSNESS	10012373
Impaired attention, cognition and mood	DISTURBANCE IN ATTENTION	10013496
Impaired attention, cognition and mood	DYSARTHRIA	10013887
Impaired attention, cognition and mood	DYSLOGIA	10054940
Impaired attention, cognition and mood	DYSPHORIA	10013954
Impaired attention, cognition and mood	EMOTIONAL DISORDER	10014551
Impaired attention, cognition and mood	EMOTIONAL POVERTY	10014557
Impaired attention, cognition and mood	EMOTIONAL DISTRESS	10049119
Impaired attention, cognition and mood	EXECUTIVE DYSFUNCTION	10070246
Impaired attention, cognition and mood	FATIGUE	10016256
Impaired attention, cognition and mood	FEELING OF DESPAIR	10016344
Impaired attention, cognition and mood	FLAT AFFECT	10016759
Impaired attention, cognition and mood	IMPAIRED DRIVING ABILITY	10049564
Impaired attention, cognition and mood	IMPAIRED REASONING	10071176
Impaired attention, cognition and mood	MEMORY IMPAIRMENT	10027175
Impaired attention, cognition and mood	MENTAL DISABILITY	10027353
Impaired attention, cognition and mood	MENTAL DISORDER	10061284
Impaired attention, cognition and mood	MENTAL IMPAIRMENT	10027374
Impaired attention, cognition and mood	MENTAL STATUS CHANGES	10048294
Impaired attention, cognition and mood	MOANING	10027783
Impaired attention, cognition and mood	MOOD ALTERED	10027940
Impaired attention, cognition and mood	NEUROLEPTIC-INDUCED DEFICIT SYNDROME	10075295
Impaired attention, cognition and mood	PREMENSTRUAL DYSPHORIC DISORDER	10051537

Impaired attention, cognition and mood	PREMENSTRUAL SYNDROME	10036618
Impaired attention, cognition and mood	PSYCHOMOTOR RETARDATION	10037213
Impaired attention, cognition and mood	PSYCHOMOTOR SKILLS IMPAIRED	10049215
Impaired attention, cognition and mood	RETROGRADE AMNESIA	10038965
Impaired attention, cognition and mood	SEDATION	10039897
Impaired attention, cognition and mood	SLOW SPEECH	10071299
Impaired attention, cognition and mood	SOMNOLENCE	10041349
Impaired attention, cognition and mood	STUPOR	10042264
Impaired attention, cognition and mood	TRANSIENT GLOBAL AMNESIA	10044380
Other abuse-related terms	ACCIDENTAL DEATH	10063746
Other abuse-related terms	ACCIDENTAL POISONING	10000383
Other abuse-related terms	ALCOHOL ABUSE	10001584
Other abuse-related terms	ALCOHOL PROBLEM	10001606
Other abuse-related terms	ALCOHOL WITHDRAWAL SYNDROME	10053164
Other abuse-related terms	ALCOHOLIC HANGOVER	10001623
Other abuse-related terms	ALCOHOLISM	10001639
Other abuse-related terms	AMPHETAMINES	10063227
Other abuse-related terms	AMPHETAMINES POSITIVE	10063228
Other abuse-related terms	ANALGESIC THERAPY	10053469
Other abuse-related terms	ANTITUSSIVE THERAPY	10055120
Other abuse-related terms	ANXIOLYTIC THERAPY	10066478
Other abuse-related terms	ATAXIA	10003591
Other abuse-related terms	BENZODIAZEPINE DRUG LEVEL	10072337
Other abuse-related terms	BINGE DRINKING	10071238
Other abuse-related terms	COMPLETED SUICIDE	10010144
Other abuse-related terms	DECREASED APPETITE	10061428
Other abuse-related terms	DOPAMINERGIC DRUG THERAPY	10072385
Other abuse-related terms	HANGOVER	10019133
Other abuse-related terms	HEADACHE	10019211
Other abuse-related terms	INCREASED APPETITE	10021654
Other abuse-related terms	INTENTIONAL SELF-INJURY	10022524
Other abuse-related terms	MIOSIS	10027646
Other abuse-related terms	MUSCLE RELAXANT THERAPY	10058909
Other abuse-related terms	MUSCLE RIGIDITY	10028330
Other abuse-related terms	MYDRIASIS	10028521
Other abuse-related terms	NASAL NECROSIS	10028747
Other abuse-related terms	NASAL SEPTUM PERFORATION	10028765
Other abuse-related terms	NASAL SEPTUM ULCERATION	10028766
Other abuse-related terms	NICOTINE DEPENDENCE	10057852
Other abuse-related terms	PARAESTHESIA	10033775
Other abuse-related terms	POISONING	10061355
Other abuse-related terms	PRESCRIBED OVERDOSE	10051076
Other abuse-related terms	PRODUCT TAMPERING	10069330

Other abuse-related terms	PRODUCT USED FOR UNKNOWN INDICATION	10070592
Other abuse-related terms	SELF-INJURIOUS IDEATION	10051154
Other abuse-related terms	SUICIDAL BEHAVIOUR	10065604
Other abuse-related terms	SUICIDAL IDEATION	10042458
Other abuse-related terms	SUICIDE ATTEMPT	10042464
Other abuse-related terms	TOBACCO ABUSE	10043903
Other abuse-related terms	TOBACCO WITHDRAWAL SYMPTOMS	10059612
Other abuse-related terms	TREATMENT NONCOMPLIANCE	10049414
Other abuse-related terms	URINE AMPHETAMINE	10059955
Other abuse-related terms	URINE AMPHETAMINE POSITIVE	10051400

Appendix 5. Analyses Not Intended for the Clinical Study Report

Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following:

Summary of AEs provided as a dataset which will be converted to an XML file. Both SAEs and ‘Other’ AEs are summarized by treatment group and by MedDRA PT.

- An AE is considered ‘Serious’ whether or not it is considered a TEAE.
- An AE is considered in the ‘Other’ category if it is both a TEAE and is not serious. For each Serious AE and ‘Other’ AE, for each term and treatment group, the following are provided:
 - the number of participants at risk of an event
 - the number of participants who experienced each event term
 - the number of events experienced.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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