Statistical Analysis Plan H8H-MC-LAHV V1

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

NCT04396236

Approval Date: 10-Jun-2020

1. Statistical Analysis Plan: H8H-MC-LAHV: Pediatric Options for Migraine Relief: A Randomized, Double Blind, Placebo Controlled Study of Lasmiditan for Acute Treatment of Migraine: PIONEER-PEDS1

Lasmiditan (LY573144)

Acute Treatment of Migraine Attacks

Study H8H-MC-LAHV is a Phase 3, multi-country, double-blind, randomized, parallel, placebo-controlled trial to assess the efficacy and safety of lasmiditan 50 mg, 100 mg, and 200 mg compared to placebo in the treatment of a single migraine attack in children and adolescents 6 to <18 years of age who have a history of migraine with or without aura as defined by International Headache Society International Classification of Headache Disorders, 3rd edition (ICHD 3) (ICHD 3 2018) diagnostic criteria 1.1 or 1.2.1.

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Protocol H8H-MC-LAHV
Phase 3

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

Approval Date: 10-Jun-2020 GMT

2. Table of Contents

Section **Page**

Table of Contents

Table **Page**

Table of Contents

Figure **Page**

Table of Contents

Appendix **Page**

3. Revision History

Statistical analysis plan (SAP) Version 1 will be approved prior to unblinding of the data by the Data Monitoring Committee (DMC).

4. Study Objectives

Table LAHV.4.1 and Table LAHV.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 LAHV.4.1 and Table LAHV.4.2.
- The handling of intercurrent events and missing data may be found in Section 6.4 and Table LAHV.6.5 of this document.
- Summary measures are described in Table LAHV.6.4 and Table LAHV.6.5.

4.1. Primary Objective

Table LAHV.4.1 shows the primary objective and endpoint of the study.

Table LAHV.4.1. Primary Objective and Endpoint

Objective	Endpoint
Primary	
To test the hypothesis that lasmiditan 200 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients ≥6 to <18 years of age	Proportion of patients ≥6 to <18 years of age with pain freedom at 2 hours after dosing

4.2. Secondary Objectives

Table LAHV.4.2 shows the secondary objectives and endpoints of the study.

Table LAHV.4.2. Secondary Objectives and Endpoints

Objectives	Endpoints
Key Secondary	
To test the hypothesis that lasmiditan 100 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients ≥6 to <18 years of age	Proportion of patients ≥6 to <18 years of age with pain freedom at 2 hours after dosing
To test the hypothesis that lasmiditan 50 mg is superior to placebo in the acute treatment of a migraine attack in pediatric patients ≥6 to <18 years of age	Proportion of patients ≥6 to <18 years of age with pain freedom at 2 hours after dosing
Secondary*	
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to pain freedom in age subgroups	Proportion of patients with pain freedom at 2 hours after dosing in the subgroup of patients ≥6 to <[CCI] years of age and in the subgroup of patients [CCI] to <18 years of age

To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to pain relief	Proportion of patients ≥6 to <18 years of age with pain relief at 2 hours after dosing
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to resolution of the MBS	Proportion of patients ≥6 to <18 years of age MBS-free at 2 hours after dosing
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to absence of individual associated symptoms of migraine	In patients ≥6 to <18 years of age: • Proportion of patients nausea-free at 2 hours after dosing • Proportion of patients photophobia-free at 2 hours after dosing • Proportion of patients phonophobia-free at 2 hours after dosing
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to sustained pain freedom	Proportion of patients ≥6 to <18 years of age with sustained pain freedom at 24 and 48 hours
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to use of additional medication within 24 and 48 hours	In patients ≥6 to <18 years of age: • Proportion of patients using additional medication for migraine within 24 and 48 hours • Time to use of additional migraine medication
CCI	
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to patient-reported global measure of change	Proportion of patients ≥6 to <18 years of age with PGIC rating of "a lot better," "better," "no different," "worse," and "a lot worse" at 2 hours
To evaluate the efficacy of lasmiditan (50 mg, 100 mg, and 200 mg) compared with placebo with respect to the degree of migraine interference in normal activities	Proportion of patients ≥6 to <18 years of age with a rating of 0 ("not at all"), 1 ("a little"), 2 ("a lot"), or 3 ("completely") at 2 hours
Acceptability of the Formulation	
To evaluate the acceptability of lasmiditan tablets (50 mg, 100 mg, and 200 mg) with respect to ease of swallowing of the tablets	Proportion of patients ≥6 to <18 years of age with a rating of "very easy," "easy," "neither easy nor hard," "hard," or "very hard" at 24 hours after dosing

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

5. Study Design

5.1. Summary of Study Design

Study H8H-MC-LAHV is a randomized, double-blind, placebo-controlled, parallel group study. The efficacy and safety of lasmiditan (50 mg, 100 mg, and 200 mg) compared to placebo will be examined in 6 to <18 year old patients with a history of migraine with or without aura. Patients will complete a double-blind placebo challenge period (Stage 1) in the first [redacted] minutes of the treated attack, with [redacted] eligible for randomization into the efficacy analysis period (Stage 2). Dosing in Stage 2 will include weight-based doses that correspond to 50 mg, 100 mg, and 200 mg adult equivalent exposures. Figure LAHV.5.1 illustrates the design.

Figure LAHV.5.1. Illustration of study design for Clinical Protocol H8H-MC-LAHV.

5.2. Determination of Sample Size

The study will have met its primary objective if a statistically significant higher proportion of patients in the lasmiditan 200 mg treatment group are pain free at the 2-hour assessment time point relative to placebo. With a sample size of [redacted] pediatric patients in the primary efficacy analysis, the lasmiditan 200 mg group has [redacted]% overall power to be statistically significant compared with placebo. The lasmiditan 50 mg and 100 mg treatment groups have [redacted]% and [redacted]% overall power, respectively, to be statistically significant relative to placebo in the proportion of

patients that are pain free at the 2-hour time point assessment. The study wise 1-sided type I error rate is controlled at a 0.025 level. Simulations were conducted to obtain the overall power values using R version 3.5.1.

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

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

Table LAHV.5.1 defines additional targets for the efficacy analysis population:

Table LAHV.5.1. Efficacy Analysis Population Targets

Number of Patients in the Efficacy Analysis Population	Characteristic
Minimum of CCI% (~CCI)	≥6 to <CCI years of age
Minimum of CCI% (~CCI)	≥CCI to <18 years of age
Similar number of patients in each group	≥CCI to <CCI years of age
	≥CCI to <CCI years of age
Minimum of CCI% of the total number of patients	Male
No more than CCI% of the total number of patients	Currently using preventive treatment of migraine defined as reported concomitant use of one or more of the following medications (See Section 6.7.1): • propranolol • topiramate • cinnarizine • amitriptyline.

5.3. Method of Assignment to Treatment

The dose to be administered to each participant, by weight, was determined by pharmacokinetic (PK) and safety data from Study LAHX. The selected dose for each weight cohort is intended to achieve exposures comparable to the 50 mg, 100 mg, and 200 mg doses of lasmiditan in adults (referred to throughout as LTN 50 mg, LTN 100 mg, and LTN 200 mg). To maintain the blind, each dose will require CCI tablets.

Table LAHV.5.2 and Table LAHV.5.3 show the planned treatment regimens, by dose, for Stage 1 and Stage 2.

CCI

CCI

Treatments will be assigned in a double-blind manner. Details on randomization and definitions of response in the placebo challenge period (Stage 1) are located within the Ethical Review Board supplement. Patients who are CCI after Stage 1 dosing will be randomized in a CCI ratio (placebo: LTN 50 mg: LTN 100 mg: LTN 200 mg) to study treatment in Stage 2. Randomization will be stratified by CCI in Stage 2 (see Section 6.7.1). Patients who are CCI will be assigned to CCI . CCI will be instructed to CCI

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.

For continuous data, descriptive statistics including the mean, standard deviation (SD), median, minimum, maximum and N (number of patients with available data) will be presented. For categorical data, frequency counts and percentages will be presented.

Treatment effects will be evaluated based on a 2-sided significance level of 0.05 for all efficacy and safety analyses unless otherwise stated. In comparisons of each lasmiditan group to placebo, no multiplicity adjustments will be made to control the overall significance level, other than for the primary efficacy endpoint, the details of which are provided in Section 6.5.

Table LAHV.6.1 gives the treatment groups and the between-group comparisons to be displayed for the analysis populations within the study period.

Table LAHV.6.1. Treatment Group Descriptions by Analysis Populations

Analysis Population	Study Period	Treatment Group Descriptions	Abbreviation	Between-Group Comparison
All Randomized Population	Enrollment, Treatment, and EOS	CCI		
Safety Population	Stage 1 and Stage 2			
Efficacy Analysis Population	Stage 2			

Abbreviations: LTN = lasmiditan; mg = miligram; PBO = placebo.

6.2. Analysis Populations

For analysis purposes, the following populations are defined in Table LAHV.6.2 and illustrated in Figure LAHV.6.1.

Table LAHV.6.2. Analysis Populations

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

Abbreviation: LTN = lasmiditan.

Figure LAHV.6.1. Analysis populations.

6.3. Adjustments for Covariates

All statistical models for the efficacy and safety endpoints will include the fixed categorical effect of treatment (placebo, LTN 50 mg, LTN 100 mg, LTN 200 mg), as well as the fixed, categorical covariates o CCI [redacted]. All mixed effects models will also include the fixed categorical effects of CCI [redacted].

When a specific endpoint is analyzed separately among patients ≥6 to <CCI years of age and CCI to <18 years of age, the covariate of CCI will be removed from the corresponding model.

6.4. Handling of Dropouts or Missing Data

CCI [redacted]

CCI

6.4.3. Tipping Point Analysis

A tipping point analysis will be used to evaluate the sensitivity of the primary and key secondary analysis outcomes and assumptions inherent in missing data imputation methods. The tipping point analysis is a special application of the multiple imputation method under the missing not at random assumption. The tipping point approach is like a progressive stress test that assesses how severe departures from the missing at random assumption must be in order to overturn conclusions. The tipping point is identified as the response probability values that leads to loss of statistical significance when evaluating the lasmiditan treatment group relative to the placebo group.

This procedure will be performed using the following steps for the proportion of patients with pain freedom at the 2-hour time point:

1. Perform treatment group comparisons versus placebo using a logistic regression model for the observed data. The model includes treatment group, CCI as covariates.
2. Perform treatment group comparisons versus placebo for the observed data and imputing missing data with the most extreme case. The most extreme case is defined as a response probability of CCI for the lasmiditan treatment groups and a response probability of CCI for the placebo treatment group. The model will be as specified in step 1. If statistical significance is retained after performing this study, no tipping point is identified, and the below steps will not be performed.
3. Perform the following steps for all combinations of the following response probabilities:
   - For the placebo group, impute different response probabilities of CCI
   - For the lasmiditan treatment groups, impute different response probabilities of CCI
     a. Create multiple datasets for each combination of the response probabilities in step 3. Impute missing data by using a Bernoulli distribution CCI
     b. Perform treatment group comparisons versus placebo for each dataset created in step 3.a. The model will be as specified in step 1.
     c. Analyses in step 3.b are aggregated across the datasets using SAS® PROC MI ANALYZE in order to compute a p-value for the treatment comparison for each combination of response probabilities.
4. As a sensitivity test, treatment group comparisons versus placebo for the confirmed responses case will be performed by imputing missing data for both the lasmiditan and placebo treatment groups as CCI The model will be as specified in Step 1.

6.4.4. Logistic Mixed Effects Model for Repeated Measures

Supportive analyses will be performed similarly to analyses described in Section 6.4.1 with the exception of censoring all time points following the administration of the additional medication for rescue.

The logistic mixed effects method may be justified when the estimand of interest uses the hypothetical strategy. The scientific question of interest is to assess the effect of study treatment in a hypothetical scenario where all patients have complete data and no patients take additional migraine medication.

6.5. Multiple Comparisons/Multiplicity

A hierarchical multiple comparisons procedure, which will control type I error in the primary endpoint analysis, will be implemented as follows. First, the hypothesis that LTN 200 mg is superior to placebo is tested at the 2-sided 0.05 significance level. If LTN 200 mg does not show a statistically significant higher proportion of patients that are pain-free at the 2-hour assessment time point relative to placebo, then no further testing is done. Otherwise, the hypothesis that LTN 100 mg is superior to placebo is then tested at the 2-sided 0.05 significance level. If LTN 100 mg does not show a statistically significant higher proportion of patients that are pain-free at the 2-hour assessment time point relative to placebo, then no further testing is done. Otherwise, the hypothesis that LTN 50 mg is superior to placebo is then tested at the 2-sided 0.05 significance level.

6.6. Patient Disposition

Patients will be summarized as illustrated in Figure LAHV.6.2.

A summary of patients randomized at each investigative site (for each Stage) and country will also be provided.

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

Figure LAHV.6.2. Disposition.

6.7. Patient Characteristics

6.7.1. Demographics

The following patient characteristics at baseline will be summarized by treatment group in the safety population and efficacy analysis population:

- Age (years)
- Age groups:
  - CCI [redacted]
- 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)
- Height (cm)
- Weight (kg)
- Weight group (CCI [redacted])
- Body mass index (BMI) (weight (kg) / [height (m)]^2)
- Geographic region (North America, Europe, Other)
- History of migraine with aura (yes, no)
- History of migraine without aura (yes, no)
- Duration of migraine history (years)
- Average number of migraine attacks per month during the past 2 months
- Average duration of an untreated migraine attack (hours)
- CCI [redacted]
- If female, menstrual status (pre-menarchal, menarchal)
- Onset of puberty status (pre-pubertal, pubertal)

Baseline for the efficacy population will be defined as the last available assessment recorded on or prior to the study medication dose in Stage 1 and in most cases will be the assessment at time point 0.

For patients who dose with lasmiditan in either Stage 1 or Stage 2, baseline for the safety population will be defined as the last available assessment recorded on or prior to the lasmiditan dose. For patients who only dose with placebo, baseline for the safety population will be defined as the last available assessment recorded on or prior to the first dose of placebo. See Table LAHV.6.6 for details.

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; height will be calculated as the average of the 3 collected measurements.

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.

For patients taking migraine preventive medication, treatment regimen is stable and has been taken for at least 3 months prior to Visit 1. While patients may report a number of interventions for preventive treatment, for this purpose, "preventive treatment" is limited to the 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).

Pubertal status will be defined as follows:

- For males, if the patients 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".

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

6.7.2. 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 illness(es) that end prior to the signing of informed consent. Pre-existing conditions are those events ongoing at the time of the enrollment visit, i.e., Visit 2. For the safety 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 LTN 200 mg 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.

6.7.3. 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 safety population by treatment group using WHO PTs listed by decreasing frequency in the LTN 200 mg treatment group. Patients with multiple occurrences of the same medication will be counted once within the corresponding PT.

6.7.4. Characteristics of Treated Migraine Attack

The following will be summarized by treatment group for the Safety Analysis and efficacy analysis populations.

- Baseline migraine severity
  - Severe
  - Moderate
  - Mild
  - None
- Baseline associated symptoms
  - Nausea
  - Phonophobia
  - Photophobia
  - None
- Baseline most bothersome symptom (MBS)
  - Nausea
  - Phonophobia
  - Photophobia
- For females of childbearing potential, menstruating at time of treated attack
  - Yes
  - No
- 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

6.8. Drug Accountability/Compliance

All patients will be dispensed CCI tablets at Visit 2 and the number of tablets returned will be recorded at the end of study (EOS) visit. At each stage in the treatment period, the dose of study drug requires taking CCI tablets.

Patients will be considered either study drug compliant as defined in Table LAHV.6.3.

Table LAHV.6.3. Study Drug Compliance by Dosing Sequence

Dosing Progression:	Study Drug Compliant if Number of Tablets Returned (i.e., accountability) is Equal to:
CCI	

The number and percentage of patients who are considered study drug compliant will be summarized by treatment group and by dosing progression for the all enrolled population.

Study drug compliance data will also be presented in a listing for the enrolled population. 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 Stage 1 and Stage 2 randomization treatment assignments will be presented for the enrolled population.

6.9. Concomitant Therapy

Concomitant medications are those taken during the study, from the screening visit (Visit 1) to 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 percentage of concomitant medication use will be summarized by treatment group for the safety population. Medications will be coded using the most current version of the WHO Drug Dictionary and sorted by decreasing frequency of PTs in the LTN 200 mg group.

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

All efficacy, medical resource utilization, and health economics analyses will be performed on the efficacy analysis population. Efficacy assessments will be collected via an CCI. Medical resource utilization and health economics assessments will be collected via an CCI and the electronic case report form (eCRF).

Baseline is defined as the last available assessment recorded on or prior to the study medication dose in Stage 1 and in most cases will be the minute assessment at time point 0. The baseline period is defined as the start of screening and ends prior to the study medication dose in Stage 1.

Table LAHV.6.4 includes the description, derivation and definition of missingness of the efficacy, medical resource utilization, and health economics measures and endpoints.

Table LAHV.6.5 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.

For all categorical efficacy, medical resource utilization, and health economics endpoints, summaries will include model estimates for the probability of response for each treatment group along with statistics for treatment group comparisons (each lasmiditan dose versus placebo). The model estimates for the probability of response will also include the standard error and 95% confidence interval (CI). Summaries will include an estimate of the difference between treatment groups with corresponding 95% CI, the odds ratio with corresponding 95% CI, and p-value.

For time to event analyses, treatment group comparisons will include Kaplan-Meier estimates, p-values, and 95% CIs from the stratified log rank tests.

Table LAHV.6.4. 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 [redacted] using a 5-Face Pain Scale at each assessment time point ([redacted] 2-hour, 24-hour, and 48-hour). Migraine pain intensity is defined as follows:  • Face 1 = no pain • Face 2 = mild pain • Faces 3 and 4 = moderate pain • Face 5 = severe pain (Maunuksela et al. 1987). The patient selects the number corresponding to the face that represents their current pain severity.	Proportion of patients with pain freedom	Number of patients 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).	Missing if assessment is missing.
		Proportion of patients with pain relief	Number of patients with a reduction in baseline pain from moderate (Faces 3 and 4) or severe (Face 5) to mild or no pain (Face 1 or 2) or patient is asleep.	Missing if assessment is missing.
		Proportion of patients with sustained pain freedom at the 24-hour time point	Number of patients pain free (Face 1) at the 2-hour and the 24-hour time points, and without the use of additional migraine medication for rescue on or before 24 hours.	Missing if the 2-hour or the 24-hour assessments is missing.
		Proportion of patients with sustained pain freedom at the 48-hour time point	Number of patients pain free (Face 1) at the 2-hour, 24-hour, and the 48-hour time points, and without the use of additional migraine medication for rescue on or before 48 hours.	Missing if the 2-hour, 24-hour, or the 48-hour assessment is missing.
Associated Symptoms of Migraine: Most Bothersome Symptom (MBS)	The associated symptoms (yes/no) of migraine will be captured in the [redacted] at each assessment time point ([redacted], 2-hour, 24-hour, and 48-hour). The associated symptoms are the following:	Proportion of patients with resolution of the MBS	Of the patients who report at least 1 associated symptom of migraine at baseline, number of patients with an absence of their MBS.	Missing if the assessment is missing.

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	• Nausea • Phonophobia • Photophobia MBS is defined as 1 of the 3 symptoms a patient may be experiencing with their qualifying migraine attack prior to dosing and is identified as follows: • For patients who report experiencing more than 1 symptom, the CCI prompts them to identify which is the MBS. • For patients who report experiencing only 1 of the symptoms, that symptom is automatically identified as the MBS.			
Associated Symptoms of Migraine: Individual Symptoms	The associated symptoms (yes/no) of migraine will be captured in CCI at each assessment time point CCI , 2-hour, 24-hour, and 48-hour). The associated symptoms are the following: • Nausea • Phonophobia • Photophobia	Proportion of patients nausea-free	Number of patients with an absence of nausea.	Missing if the assessment is missing.
		Proportion of patients with resolution of nausea	Of the patients who report nausea as an associated symptom of migraine at baseline, number of patients with an absence of nausea.	Missing if the assessment is missing.
		Proportion of patients phonophobia-free	Of the patients who report phonophobia as an associated symptom of migraine at baseline, number of patients with an absence of phonophobia.	Missing if the assessment is missing.
		Proportion of patients with resolution of phonophobia	Number of patients with an absence of phonophobia.	Missing if the assessment is missing.
		Proportion of patients	Of the patients who report photophobia as an associated	Missing if the assessment is missing.

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		photophobia-free	symptom of migraine at baseline, number of patients with an absence of photophobia.	
		Proportion of patients with resolution of photophobia	Number of patients with an absence of photophobia.	Missing if the assessment is missing.
Additional Migraine Treatment for Rescue	CCI will remind patients that additional medication for pain and symptoms of migraine is permitted after completion of 2-hour assessment time point. Use of additional treatment for migraine will be recorded by the patient in the CCI and captured in the concomitant medication eCRF at the EOS visit.	Proportion of patients using additional migraine medication for rescue within 24 hours	Number of patients reporting a concomitant medication with an indication for use = "acute migraine treatment" and with a start date and time that is within 24 hours of the administering Stage 2 study medication.	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 24 hours of administering Stage 2 study medication.
		Proportion of patients using additional migraine medication within 48 hours	Number of patients reporting 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 Stage 2 study medication.	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

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
				hours of administering Stage 2 study medication.
		Time to use of additional migraine medication (hours)	Date and time of the first (in chronological time) reported concomitant medication with an indication for use = "acute migraine treatment" minus the date and time of administration of Stage 2 study medication.	Missing start date/time will be imputed by following the rules in Appendix 1. If after applying the imputation rules, the start date/time is still missing then the medication start time will be the time of administering Stage 2 study medication.
Interference in Daily Activities	A 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 (CCI 2-hour, 24-hour, and 48-hour): 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.	Shift from baseline to postbaseline in interference in daily activities rating	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 the assessment is missing.
		Proportion of	Number of patients reporting	Missing if the assessment

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
		patients with an interference in daily activities rating of 0 (not at all)	a rating of 0 (not at all).	is missing.
		Proportion of patients with an 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).	Missing if the assessment is missing.
		Proportion of patients with an interference in daily activities rating of 0 (not at all), 1 (a little), or 2 (a lot)	Number of patients reporting a rating of 0 (not at all), 1 (a little), or 2 (a lot).	Missing if the assessment is missing.
Patient Global Impression of Change (PGIC)	Patients will be asked at the 2-hour assessment time point the question, "How did the medicine make you feel?" using a 5-point Likert scale: 1. a lot better, 2. better, 3. no different, 4. worse, 5. a lot worse (Guy 1976).	Proportion of patients with a rating of "a lot better"	Number of patients reporting a rating of "a lot better."	Missing if the assessment is missing.
		Proportion of patients with a rating of "better" or	Number of patients reporting a rating of "better" or "better."	Missing if the assessment is missing.

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	The PGIC represents a global assessment of effects of the study medication on multiple outcomes, including • migraine pain • associated symptoms • side effects, and • function (Geisser et al. 2010; Scott and McCracken 2015).	"better"		
		Proportion of patients with a rating of "a lot better"	Number of patients reporting a rating of "a lot better."	Missing if the assessment is missing.
		Proportion of patients with a rating of "no different"	Number of patients reporting a rating of "no different."	Missing if the assessment is missing.
		Proportion of patients with a rating of "worse"	Number of patients reporting a rating of "worse."	Missing if the assessment is missing.
		Proportion of patients with a rating of "a lot worse"	Number of patients reporting a rating of "a lot worse."	Missing if the assessment is missing.
		Proportion of patients with a rating of "worse" or "a lot worse"	Number of patients reporting a rating of "worse" or "a lot worse."	Missing if the assessment is missing.
Acceptability of lasmiditan Tablets (ease of swallowing)	The patient will be asked to provide responses to a question designed to assess the patient's ability to swallow the tablet at the 24-hour assessment time point in CCI . The scale includes both a hedonic and Likert-type response scale to assist children and adolescents in providing a response to the following: "Think about the experience of swallowing the study medicine. How easy or hard was it for you to swallow one of the pills?"	Proportion of patients with a rating of "very easy"	Number of patients randomized to lasmiditan and reporting a rating of "very easy."	Missing if the assessment is missing.
		Proportion of patients with a rating of "easy"	Number of patients randomized to lasmiditan and reporting a rating of "easy."	Missing if the assessment is missing.
		Proportion of patients with	Number of patients randomized to lasmiditan	Missing if the assessment is missing.

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	☐  Very easy ☐  Easy ☐  Neither Easy nor Hard ☐  Hard ☐  Very Hard	a rating of "very easy" or "easy"	and reporting a rating of "very easy" or "easy."	
		Proportion of patients with a rating of "neither easy or hard"	Number of patients randomized to lasmiditan and reporting a rating of "neither easy or hard."	Missing if the assessment is missing.
		Proportion of patients with a rating of "hard"	Number of patients randomized to lasmiditan and reporting a rating of "hard."	Missing if the assessment is missing.
		Proportion of patients with a rating of "very hard"	Number of patients randomized to lasmiditan and reporting a rating of "very hard."	Missing if the assessment is missing.
		Proportion of patients with a rating of "hard" or "very hard"	Number of patients randomized to lasmiditan and reporting a rating of "hard" or "very hard."	Missing if the assessment is missing.
Pediatric Migraine Disability Assessment Scale (PedMIDAS)	The PedMIDAS captures disability due to migraine at screening in the eCRF. 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	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 any item is missing.
		Total number of days with a headache, in the last 3 months	Number of days with a headache.	Missing if assessment is missing.
		Headache	Score associated with the	Missing if assessment is

Measure	Description	Endpoint	Derivation/Comment	Definition of Missing
	5. inability to participate in extracurricular and leisure activities, and 6. 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. 1. On how many days in the last 3 months did you have a headache? 2. 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)	pain	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.

Table LAHV.6.5. Description of Efficacy, Medical Resource Utilization, and Health Economics Analysis

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
Migraine Pain Severity	Proportion of patients with pain freedom	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO	2-hour	Primary
				LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Key Secondary
				LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI	Secondary
			Tipping Point Analysis	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Sensitivity
			Logistic Mixed Effects Model	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Supportive
		modified Efficacy Analysis Population	Bayesian Analysis (see Section 6.10.2.3)	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
	Proportion of patients with pain relief	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
	Proportion of patients with sustained pain freedom at the 24-hour time point	Efficacy Analysis Population	Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	24-hour	Secondary
	Proportion of patients with Sustained pain freedom at the 48-hour time point	Efficacy Analysis Population	Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	48-hour	Secondary
Associated Symptoms of Migraine: Most Bothersome Symptom	Proportion of patients with resolution of the most bothersome symptom (MBS)	Efficacy Analysis Population – patients who reported at least 1 associated symptom of migraine at baseline	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary
Associated Symptoms of Migraine: Individual Symptoms	Proportion of patients nausea-free	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary
	Proportion of patients with resolution of nausea	Efficacy Analysis Population – patients who reported nausea at baseline	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary
	Proportion of patients phonophobia-free	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary
	Proportion of	Efficacy Analysis	Logistic Mixed	LTN 200mg vs.	CCI	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
	patients with resolution of phonophobia	Population – patients who reported phonophobia at baseline	Effects Model with CCI	PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	
	Proportion of patients photophobia-free	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary
	Proportion of patients with resolution of photophobia	Efficacy Analysis Population – patients who reported photophobia at baseline	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	CCI 2-hour	Secondary
Additional Migraine Treatment for Recuse	Proportion of patients using additional migraine medication for rescue within 24 hours	Efficacy Analysis Population	Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	24 hours of administering Stage 2 study medication	Secondary
	Proportion of patients using additional migraine medication within 48 hours	Efficacy Analysis Population	Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	48 hours of administering Stage 2 study medication	Secondary
	Time to use of additional migraine medication	Efficacy Analysis Population	Kaplan Meier (stratified log-rank test)	LTN 200mg vs. PBO LTN 100mg vs. PBO	Stage 2 of the Treatment Period	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
	(hours)			LTN 50mg vs. PBO		
Interference in Daily Activities	Shift from baseline to postbaseline in interference in daily activities rating	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
	Proportion of patients with a rating of 0 (not at all)	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
	Proportion of patients with a rating of 0 (not at all) or 1 (a little)	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
	Proportion of patients with a rating of 0 (not at all), 1 (a little), or	Efficacy Analysis Population	Logistic Mixed Effects Model with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO	2-hour	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
	2 (a lot)			LTN 50mg vs. PBO		
			CCI			
Patient Global Impression of Change (PGIC)	Proportion of patients with a rating of "a lot better"	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
		Efficacy Analysis Population	Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
	Proportion of patients with a rating of "a lot better" or "better"	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
		Efficacy Analysis Population	Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
	Proportion of patients with a rating of "better"	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
	Proportion of patients with a rating of "no different"	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
	Proportion of	Efficacy Analysis	Summary	Not applicable	2-hour	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
	patients with a rating of "worse"	Population	statistics, observed			
	Proportion of patients with a rating of "a lot worse"	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
			Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
	Proportion of patients with a rating of "worse" or "a lot worse"	Efficacy Analysis Population	Summary statistics, observed	Not applicable	2-hour	Secondary
			Logistic Regression with CCI	LTN 200mg vs. PBO LTN 100mg vs. PBO LTN 50mg vs. PBO	2-hour	Secondary
Acceptability of lasmiditan tablets (ease of swallowing)	Proportion of patients with a rating of "very easy"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	By tablet strength (no inferential statistics)	24-hour	Secondary
	Proportion of patients with a rating of "easy"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	By tablet strength (no inferential statistics)	24-hour	Secondary
	Proportion of patients with a rating of "very easy" or "easy"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	By tablet strength (no inferential statistics)	24-hour	Secondary

Measure	Endpoint	Population (Section 6.2)	Analysis Method (Section 6.4 and 6.10)	Comparisons	Assessment Time Points	Analysis Type
	Proportion of patients with a rating of "neither easy or hard"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	Not applicable	24-hour	Secondary
	Proportion of patients with a rating of "hard"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	Not applicable	24-hour	Secondary
	Proportion of patients with a rating of "very hard"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	Not applicable	24-hour	Secondary
	Proportion of patients with a rating of "hard" or "very hard"	Efficacy Analysis Population – patients randomized to lasmiditan	Summary statistics, observed	Not applicable	24-hour	Secondary
CCI						

Abbreviations: LTN = lasmiditan; mg = milligrams; CCI [redacted]; PBO = placebo.

6.10.1. Methodology for Primary Analysis

The primary analysis will be performed using a logistic mixed effects model as a pseudo-likelihood-based mixed effects repeated measures analysis. The analysis will include the fixed categorical effects of treatment group (placebo, LTN 50 mg, LTN 100 mg, LTN 200 mg), assessment time point (CCI [redacted], and 2-hour), and treatment-by-assessment time point interaction, as well as the fixed, categorical covariates of CCI [redacted]

The covariance structure to model the within-patient errors will be unstructured. If the unstructured covariance matrix results in a lack of convergence, the model will be fit using covariance matrices of the following order until convergence is met:

- Fisher scoring algorithm
- Heterogeneous Toeplitz
- Heterogeneous First-order autoregressive
- Toeplitz
- First-order autoregressive

The Kenward-Roger method (Kenward and Roger 1997) will be used to estimate the denominator degrees of freedom when the unstructured covariance matrix is utilized. Otherwise, the sandwich estimator (Diggle, Liang, and Zeger 1994) will be used to estimate the standard errors of the fixed effect parameters and the denominator degrees of freedom will be partitioned into between-patient and within-patient portions.

Patients who treat their migraine with additional migraine medication for rescue will be classified as a nonresponder (nonresponder imputation) for all time points following the administration of the additional medication (see Section 6.4.1).

6.10.2. Methodology for Secondary Analyses

6.10.2.1. Kaplan Meier Analyses

Time to event endpoints will be assessed using a Kaplan-Meier analysis, for which Kaplan-Meier curves will be presented by treatment group. Treatment group comparisons will be conducted using a stratified log-rank test, stratifying on CCI [redacted] Patients who not experience the event of interest will be censored 48 hours after their study medication dose in Stage 2. The estimated probability of experiencing the event of interest and corresponding 95% CI will be presented for the CCI [redacted], 2, 24, and 48 hours assessment time points. The number of patients experiencing the event of interest and the number of patients censored will be summarized by treatment group. Additionally, the Kaplan-Meier estimates and 95% CIs for the time that CCI [redacted]%, CCI [redacted]%, and CCI [redacted]% of patients experienced the event of interest will be presented.

6.10.2.2. Logistic Regression Analyses

Secondary analyses for categorical efficacy, medical resource utilization, and health economics that are assessed at single time points will use a logistic regression model that includes treatment group (placebo, LTN 50 mg, LTN 100 mg, LTN 200 mg), age group (6 to <CCI years of age, CCI to <18 years of age), and CCI as covariates. Missing data will be imputed using the CCI method (see Section 6.4.2).

6.10.2.3. Bayesian Secondary Analysis of Primary Endpoint

A Bayesian secondary analysis will be performed to facilitate borrowing of placebo information from historical studies. This approach involves the use of an informative prior that incorporates the historical control data based on a hierarchical model approach (Viele 2014). The informative prior will be incorporated into the observed placebo 2-hour pain freedom rates for Study LAHV. The historical control data will be obtained from the following 3 placebo-controlled pediatric acute migraine trials also utilizing a placebo run-in enrichment design: Ho et al. (2012), Derosier et al. (2012), and Winner et al. (2016). A sensitivity analysis is performed to determine the hyperparameters of the informative prior that would allow a flexible amount of borrowing depending on the similarity between the placebo arm of Study LAHV and the historical studies. The Bayesian analysis will be performed on the modified evaluable population defined as the efficacy analysis population plus summary level placebo 2-hour pain freedom rates from the historical data.

Further details on the sensitivity analysis is described in Appendix 2.

6.11. Safety Analyses

Baseline for safety analyses is defined for each treatment group in Table LAHV.6.6. The baseline period is defined as the start of screening and ends prior to the study medication dose in Stage 1 or Stage 2 in accordance with Table LAHV.6.6. Change from baseline will be calculated as the postbaseline value minus the baseline value.

Table LAHV.6.6. Baseline Definition for Safety Analyses

Treatment Group Description	Abbreviation	Baseline is defined as the last available assessment recorded on or prior to the study medication dose in …
CCI		

Abbreviation: LTN = lasmiditan.

Safety will be assessed by summarizing and analyzing the following:

- adverse events (AEs), including, treatment-emergent AEs (TEAEs) and serious AEs (SAEs);
- [redacted]
- vital signs (blood pressure [BP], pulse, and body temperature);
- [redacted]
- cognition (Cogstate Pediatric Brief Battery);
- growth and development (height, weight, onset of puberty, and menstrual status for females);
- safety topics of special interest.

Unless otherwise stated, treatment group comparisons (see Table LAHV.6.1) for categorical safety data will be performed using the Fisher's exact test. Summaries will include an estimate of the difference between treatment groups, corresponding 95% CI, and p-value. For AEs, statistical comparisons will be applied at each MedDRA level (that is, SOC, and PT). Continuous data will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment and baseline value as covariates. Summaries will include the least square (LS) means, an estimate of the difference between treatments, corresponding 95% CI, and p-value. However, p-values should not be over-interpreted for safety analyses.

6.11.1. Analysis of Adverse Events

6.11.1.1. Definitions

Adverse events are defined as follows:

- any untoward medical occurrences in a patient treated with study drug, 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 study medication. For patients who receive placebo in Stage 1 and lasmiditan in Stage 2, AEs that first occurred or worsened in severity while on placebo in Stage 1 will not be considered treatment-emergent. For each TEAE, the reported severity level of the event will be determined by patient or physician opinion. Adverse events that are missing severity will be considered treatment-emergent if they occurred within the time period for considering an AE as a TEAE. 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.

6.11.1.2. Analyses

In an overview table, the number and percentage of patients who reported an AE, TEAE (including by maximum severity), SAE, died, or discontinued due to an AE will be summarized and analyzed.

The number and percentage of patients who report TEAEs will be summarized and analyzed using MedDRA PTs listed by decreasing frequency in the lasmiditan 200 mg group, nested within SOC, where SOCs will be listed alphabetically. Where applicable, statistical comparisons will be applied at both the SOC and PT levels.

The following will be summarized and analyzed using MedDRA PTs listed by decreasing frequency in the lasmiditan 200 mg group:

- The number and percentage of patients who report AEs.
- The number and percentage of patients who report TEAEs.
- The number and percentage of patients with TEAEs by maximum severity. For each patient and TEAE, the 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. Adverse events 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.
- The number and percentage of patients with TEAEs that are related to study drug.
- The number and percentage of patients who report an SAE.
- The number and percentage of patients with SAEs that are related to study drug.
- The number and percentage of patients who discontinued from study due to AE.
- The number and percentage of patients who discontinued from study due to TEAE.

For events that are gender-specific, the denominator and computation of the percentage will include only patients 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.

6.11.2. Clinical Laboratory Evaluation

Clinical laboratory parameters are collected at Screening and at EOS or early discontinuation and are not temporally related to lasmiditan dosing. Age appropriate normal laboratory ranges and clinical measurements will be used. Box and whisker plots for observed and change from baseline values will be presented for laboratory parameters at Screening and at the EOS visit.

In addition, the number and percentage of patients with treatment-emergent abnormal, high, or low results based on age appropriate reference ranges at Screening and at EOS will be summarized and analyzed for each parameter. A low result is defined as a change from a value greater than or equal to the low limit at Screening to a value less than the low limit at EOS. A high result is defined as a change from a value less than or equal to the high limit at Screening to a value greater than the high limit at EOS. 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.

6.11.3. Vital Signs

Vital signs will be collected at Screening and at EOS or early discontinuation and are not temporally related to lasmiditan dosing.

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. Box and whisker plots for observed and change from baseline values will be presented for vital sign parameters at baseline and the EOS visit.

Shift tables will be produced in accordance with the Lilly-defined criteria displayed in Table LAHV.6.7. Scheduled visits, unscheduled visits, and repeat measurements will be included.

Table LAHV.6.7. 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.

6.11.5. Cognition

6.11.5.1. Possible Effects on Mental Ability

The number and percentage of patients who report AEs and TEAEs that represent possible effects on mental ability (see Appendix 3) will be summarized using PTs from the latest version of MedDRA nested within SOC, where SOCs will be listed alphabetically.

6.11.5.2. Cogstate Pediatric Brief Battery

The Cogstate Pediatric Brief Battery (© 2018 Cogstate Ltd.) is administered at the enrollment visit (Visit 2) and serves as the baseline for the comprehensive assessments in the 12-month open-label extension study, H8H-MC-LAHW (LAHW). A summary of the following 4 test scores (see Table LAHV.6.8) will be produced:

Table LAHV.6.8. 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

6.11.6. Growth and Development

Growth and development measures will be collected at Screening and at EOS. 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, at baseline and at the EOS visit, and change from baseline values for the parameters will be summarized and analyzed. Additionally, standardized summaries (including percentiles and Z-scores) will be performed at Screening according to the National Center for Health Statistics (NCHS) growth curve standards for height, weight, and BMI.

6.11.7. Menstrual Status

For female patients, the onset of menstruation (yes/no) will be collected at Screening and at EOS. Female patients who are menarchal at Screening, will be asked if they are menstruating (yes/no) at the time they dose in Stage 1. The number and proportion of female patients who shift from pre-menarchal at Screening and menarchal at EOS will be summarized. Additionally, the number and proportion of female patients who are menarchal at Screening and report that they are menstruating at the time of Stage 1 dosing will be summarized.

6.11.8. 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.

6.11.8.1. 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 and analyzed (MedDRA PTs will be sorted by decreasing frequency in the lasmiditan 200 mg group):

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

6.11.8.2. Hepatic Safety

Hepatic shift tables will be produced for postbaseline elevations from the maximum measurement in the baseline period (Section 6.11). 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 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 4 subsets described above for ALP.

6.11.8.3. 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.

Among patients with at least 1 AE in the 'Injury, Poisoning, and Procedural Complications' SOC, the number and percentage of patients who reported AEs in this SOC will be summarized using MedDRA PTs sorted by decreasing frequency in the lasmiditan 200 mg group. For each AE in this summary, the number and percentage of patients who reported 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.

6.11.8.4. 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 and analyzed:

- For patients [CCI] to <18 years of age, TEAEs within the 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 <[CCI] 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 analyses will be performed for patients [CCI] to <18 years of age:

- Time to onset and duration of key individual abuse liability (AL) TEAEs will be summarized, analyzed, and plotted. AL 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 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.

6.11.8.5. Suicide-Related Thoughts and Behaviors

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

Suicidal ideation, suicidal behaviour, and self-injurious behaviour without suicidal intent, based on the Columbia-Suicide Severity Rating Scale (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.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring postbaseline, based on the C-SSRS, will be summarized and analyzed. In particular, patients who experience at least 1 of the various composite measures and who experience any individual component will be summarized and analyzed. The composite measures are defined below:

- 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
  - wish to be dead
- suicidal behavior such as
  - completed suicide
  - nonfatal suicidal attempts
  - interrupted attempts
  - aborted attempts
  - preparatory acts or behavior
- 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

6.11.8.5.2. 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.

6.11.8.5.3. Standardized MedDRA Query (SMQ)

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

6.11.8.6. Potential Hypersensitivity Events

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:

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

- Angioedema SMQ (20000024; narrow and broad)

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:

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

6.11.8.7. 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 administered assessment.

6.12. Protocol Deviations

Important protocol deviations are defined as follows:

- Not meeting all inclusion or exclusion criteria
- Not obtaining informed consent or ascent
- Discontinuation criteria met but did not discontinue
- Not reporting a SAE appropriately (i.e., within 24 hours)
- Missing laboratory result/s
- Missing urine or serum pregnancy test
- Missing CCI [redacted] results not reviewed by the principal investigator
- Weight missing at Visit 1
- Site over or under dosed patient (provided wrong CCI [redacted])
- Patient over or under dosed patient
- Improper destruction/return of study medication
- Study medication lost or stolen
- C-SSRS administered inappropriately

Protocol deviations will be listed for the enrolled population.

6.13. Subgroup Analyses

6.13.1. Efficacy Subgroup Analyses

Subgroup analyses for efficacy, medical resource utilization, and health economics measures will be conducted using similar modeling approaches as described in Sections 6.10.1 and 6.10.2.

Analyses using a logistic mixed effects model will include fixed categorical effects for treatment, assessment time point, subgroup, treatment-by-assessment time point, treatment-by-subgroup, subgroup-by-assessment time point, and treatment-by-subgroup-by assessment time point. Treatment-by-subgroup-by-assessment time point interactions will be tested at the significance level of 0.10.

Time-to-event analyses will use a cox proportional hazard model including treatment, subgroup, and treatment-by-subgroup as covariates. Treatment-by-subgroup interactions will be tested as the significance level of 0.10.

Analyses using a logistic regression model will include treatment, subgroup, and treatment-by-subgroup as covariates. Treatment-by-subgroup interactions will be tested as the significance level of 0.10.

If any category within the subgroup is <10% of the total population, only descriptive statistics will be provided for that subgroup (that is, no inferential testing).

Table LAHV.6.9 provides definitions for each subgroup and what endpoints are to be analyzed.

Table LAHV.6.9. Definition of Subgroups and Endpoints to be Analyzed

Subgroup	Categories	Endpoints to be Analyzed	Analysis Type
Age	CCI	All endpoints described in Table LAHV.6.4 and Table LAHV.6.5	Secondary

CCI

Additional subgroup analyses on efficacy may be performed as deemed appropriate and necessary.

6.13.2. Safety Subgroup Analyses

Subgroup analyses for all safety endpoints will be conducted for CCI and analyses will be conducted similarly to those described in Section 6.11.

Interactions will be tested for categorical data using a logistic regression model that includes treatment, subgroup, and subgroup-by-treatment as covariates. Interactions for continuous data will be tested using an ANCOVA model with treatment, subgroup, and subgroup-by-treatment as covariates. Treatment-by-subgroup interactions will be tested at the significance level of 0.10.

6.14. Interim Analyses and Data Monitoring

A 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. Access to the unblinded data will be limited to the DMC and the unblinded statistician who conducts the analyses. The unblinded statistician conducting the analyses will be independent from the study team; the blinded study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded safety analyses. Study sites will receive information about the results ONLY if they need to know for the safety of their patients.

The first DMC analysis for safety may be performed 6 months after first patient visit has occurred. 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. Unblinding Plan

Refer to the H8H-MC-LAHV Blinding and Unblinding Plan.

8. References

Bretz F, Pinheiro JC, Branson M. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*. 2005; 61:738-748.

Derosier FJ, Lewis D, Hershey AD, Winner PK, Pearlman E, Rothner AD, Linder SL, Goodman DK, Jimenez TB, Granberry WK, Runken MC. Randomized trial of sumatriptan and naproxen sodium combination in adolescent migraine. *Pediatrics*. 2012;129(6):e1411-e1420.

Diggle PJ, Liang KY, Zeger SL. Analysis of Longitudinal Data. Oxford: Clarendon Press; 1994.

[FDA] Food and Drug Administration. Guidance for industry: assessment of abuse potential of drugs. 2017. Retrieved from https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.

[FDA] Food and Drug Administration: Office of Clinical Pharmacology Division of Pharmacometrics. Request for qualification of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty. 2015. https://www.fda.gov/media/99313/download.

[FDA] United States Food and Drug Administration. (Feb 2018). Migraine: developing drugs for acute treatment. Retrieved from https://www.fdanews.com/ext/resources/files/2018/02-15-18-Guidances.pdf?1520798582.

Geisser ME, Clauw DJ, Strand V, Gendreau RM, Palmer R, Williams DA. Contributions of change in clinical status parameters to Patient Global Impression of Change (PGIC) scores among persons with fibromyalgia treated with milnacipran. *Pain.* 2010;149(2):373-378.

Gould, A. Lawrence. BMA‐Mod: A Bayesian model averaging strategy for determining dose‐response relationships in the presence of model uncertainty. *Biometrical J.* 2019;61(5):1141-1159.

Guy W. ECDEU Assessment Manual for Psychopharmacology. Rockville, MD: US Dept. of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs. 1976:p 217-222.

Hershey AD, Powers SW, Vockell AL, LeCates S, Kabbouche MA, Maynard MK. PedMIDAS: development of a questionnaire to assess disability of migraines in children. *Neurology*. 2001;57(11):2034-2039.

Ho TW, Pearlman E, Lewis D, Hamalainen M, Connor K, Michelson D, Zhang Y, Assaid C, Mozley LH, Strickler N, Bachman R, Mahoney E, Lines C, Hewitt DJ. Efficacy and tolerability of rizatriptan in pediatric migraineurs: Results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design. *Cephalagia.* 2012;32(10):750-765.

International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (Nov. 2019). Addendum on estimands and sensitivity analysis in clinical trials to the Guideline on Statistical Principles for Clinical Trials [E9(R1)]. Retrieved from https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf.

International Headache Society International Classification of Headache Disorders, 3rd edition; *Cephalalgia.* 2018, Vol. 38(1) 1–211. Retrieved from https://www.ichd-3.org/wp-content/uploads/2018/01/The-International-Classification-of-Headache-Disorders-3rd-Edition-2018.pdf.

Kenward MG, Roger JH. Small sample inference for fixed effects estimators from restricted maximum likelihood. *Biometrics*. 1997;53:983-997.

Little RJA, Rubin DB. Statistical Analysis with Missing Data, 2nd edition. Hoboken, NJ:Wiley; 2002.

Maunuksela EL, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioral assessment. *Clin Pharmacol Ther.* 1987;42(2):137-141.

Scott W, McCracken LM. Patients' impression of change following treatment for chronic pain: global, specific, a single dimension, or many? *J Pain.* 2015;16(6):518-526.

Stewart WF, Lipton RB, Whyte J, Dowson A, Kolodner K, Liberman JN, Sawyer J. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology*. 1999;53(5):988 994.

Szperka, CL, VanderPluym, JH, Oakley CB. Pharmacologic acute and preventive treatment for migraine in children and adolescents. *JAMA Neurology*. December 9, 2019. doi: 10.1001/jamaneurol.2019.4170.

Viele K, Berry S, Neuenschwander B, Amzal B, Chen F, Enas N, Hobbs B, et al. Use of historical control data for assessing treatment effects in clinical trials. *Pharm Stat*. 2014;13(1):41-54.

Winner P, Farkas V, Stillova H, Woodruff B, Liss C, Lillieborg S, Raines S. Efficacy and tolerability of zolmitriptan nasal spray for the treatment of acute migraine in adolescents: results of a randomized, double-blind, multi-center, parallel-group study (TEENZ). *Headache*. 2016;56:1107-1119.

9. Appendices

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 ≥ 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 ≥ 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 ≥ study drug dose date/time,

AE start date/time	AE stop date/time	AE imputation rule, to follow in order
		then considered a TEAE.
	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. Bayesian Analysis Model for Sensitivity Analysis and Implementation Details

Sensitivity Analysis Using Bayesian Approach

The Bayesian secondary analysis utilizes an informative prior for the observed placebo 2-hour pain freedom. The historical control data will be obtained from the following 3 trials: Ho et al. (2012), Derosier et al. (2012), and Winner et al. (2016). A Bayesian sensitivity analysis is performed in order to determine the informative prior for borrowing of the placebo information. As the endpoint only involves the pain freedom at 2-hours after dosing, the sensitivity analysis focuses on a time-fixed setting solely based on pain free at 2 hours after dosing.

Historical Studies

Similarly to Study LAHV, Ho et al. (2012), Derosier et al. (2012), and Winner et al. (2016) are randomized, placebo-controlled, parallel-group pediatric acute migraine trials with a placebo run-in period, where placebo non-responders were subsequently randomized in a second period to study drug and assessed for efficacy, including pain freedom at 2-hours after dosing. In these 3 studies, the 2-hour pain freedom rates for patients randomized to placebo in the second period are included in the table below.

Study	Age Group	Number of Placebo Patients with Pain Freedom at 2-hours	Number of Placebo Patients	Placebo 2-hour Pain Freedom Rate
Ho et al. (2012)	6-17	94	388	24.2%
Derosier et al. (2012)	12-17	14	142	9.9%
Winner et al. (2016)	12-17	42	253	16.6%

Model Specification

Let y_i be a binary indicator, y_i equals 1 if patient i achieves success (i.e., the patient experiences pain freedom at 2-hours after dosing) and equals 0 otherwise. The probability of success for the patient i, is denoted by p_i. The following logistic regression model is assumed to fit p_i based on the treatment assignments:

where:

The placebo response depends on [redacted] quantify the log-odds ratios of pain freedom at 2-hours after dosing for LTN 50 mg, LTN 100 mg and LTN 200 mg as compared to placebo respectively. The primary analysis only involves the pain freedom status of LTN 200 mg and therefore the operating characteristics would only be based on β_3.

Prior Specification

The full specification of the analysis model requires the specification of prior distributions of the unknown parameters in the model, [redacted]). Following Viele et al. (2014), a shared framework is imposed on the true response rate in placebo arm of Study LAHV as well as on the placebo arms of the historical studies.

Specifically, let [redacted] denote the log odds of 2-hour pain freedom for placebo patients in i^{th} historical study. It is assumed that,

[redacted]

where, μ and τ denote the between study mean and standard deviation. A uniform hyper prior model with high variance is assumed for the mean parameter [redacted] A uniform hyper-prior model is assumed for the between study standard deviation, [redacted]. The choice of τ^* is crucial in determining the extent of borrowing and it will be discussed in the following section.

For the lasmiditan arms, [redacted]; independent diffuse (no borrowing) normal priors are assumed:

[redacted]

Determination of Variance Hyperparameter (τ^*)

The upper bound of the uniform hyper prior for the standard deviation parameter τ, τ^* controls the amount of borrowing from the 3 historical pediatric acute migraine trials, where smaller values are indicative of a higher degree of borrowing and vice versa. A simulation study is performed to determine the choice of τ^* to be used in the Bayesian analysis.

Seven choices of prior distributions for τ are considered for comparison: CCI on the basis of their performance in four different trial operating characteristics based on the LTN 200 mg dose arm:

CCI

Figure 1.1 consists of four panels displaying the performance metrics against the true placebo response rates in Study LAHV ranging from CCI% to CCI%. The informative prior of CCI was determined to be optimal due to its overall better performance as compared to other informative priors. The false positive rate CCI is CCI when the true placebo rate is less than CCI% and it does not exceed the CCI% threshold under a very high placebo response up to CCI%. In the scenario of true treatment difference of CCI in the

LTN 50 mg, LTN 100 mg, and LTN 200 mg arms, [redacted] observes higher power than the diffuse prior as long as the true placebo response is higher than [redacted]% and the power difference grows up to [redacted]% when true placebo rate nears [redacted]%. Moreover, with the choice of [redacted] the borrowing on the control arm comes with negligible amount of bias and a small standard error reduction in the estimation of treatment difference when compared with the diffuse prior.

Appendix 3. 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
Amnestic 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 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, by MedDRA PT.

- An AE is considered 'Serious' whether or not it is 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.
- Consistent with www.ClinicalTrials.gov requirements, 'Other' AEs that occur in fewer than 5% of patients in every treatment group may not be included if a 5% threshold is chosen.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

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