H8H-MC-LAIJ Statistical Analysis Plan v2

Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks

NCT03670810

Approval Date:23-Jul-2020

# 1. Statistical Analysis Plan: H8H-MC-LAIJ: Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks



Lasmiditan (LY573144) Migraine Attacks

Study H8H-MC-LAIJ is a prospective, multicenter, randomized, double-blind, modified parallel, placebo-controlled Phase 3 study of adult patients suffering from migraine with or without aura. This study will assess the efficacy, consistency of response, and safety of lasmiditan 200 mg and 100 mg compared to placebo in acute treatment of 4 migraine attacks with or without aura.


Eli Lilly and Company
Indianapolis, Indiana USA 46285


Protocol H8H-MC-LAIJ
Phase 3

Statistical Analysis Plan electronically signed and approved by Lilly: 01 July 2019
Statistical Analysis Plan Version 2 electronically signed and approved by Lilly on date provided below.

Approval Date: 23-Jul-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 was approved on 01 July 2019, which was before study unblinding, and SAP version 2 was also approved before study unblinding. The overall changes and rationale for the changes incorporated in version 2 are as follows:

- Details around the graphical method used to control for multiplicity have been added. These include alpha spending on primary and gated secondary tests and alpha sharing between tests.

- Overall edits to the original version to improve clarity of previously ambiguous topics including the various analysis populations (intent-to-treat (ITT), ITT consistency, modified intent-to-treat (mITT), and mITT consistency populations) and the triptan insufficient responder group analyses.

# 4. Study Objectives

## 4.1. Primary Objectives

The primary objective is to evaluate the efficacy of lasmiditan (LY573144) 200 mg and 100 mg compared to placebo on migraine headache pain freedom. The primary endpoint is the proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack.

The coprimary objective is to evaluate the consistency of response to lasmiditan 200 mg and 100 mg compared to placebo. The coprimary endpoint is the proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 2 out of 3 attacks.

## 4.2. Secondary Objectives

The first part of the secondary objectives is to evaluate the efficacy of lasmiditan 200 mg and 100 mg compared to placebo during the **first attack** on the following:

- freedom from migraine-associated most bothersome symptom (MBS; for example, nausea, photophobia, and phonophobia) at 2 hours postdose
- pain relief in each group at 2 hours postdose
- sustained freedom up to 24-hours and up to 48-hours
- need for rescue medication
- presence of associated migraine symptoms at 2 hours postdose, including each of the following: phonophobia, photophobia, nausea, and vomiting
- probability of migraine relapse at 24 and 48 hours
- time course of lasmiditan efficacy (pain freedom, pain relief, freedom from MBS, and no disability)
- patient global impression of change (PGIC) at 2 hours
- disability at 2 hours postdose
- health utility measured by the EuroQol 5-dimension 5-level scale (EQ-5D-5L), at 24 hours postdose
- Migraine Quality of Life Questionnaire (MQoLQ) for domains of social functioning, migraine symptoms, and feelings/concerns at 24 hours postdose
- efficacy of lasmiditan in triptan insufficient responders

The second part of the secondary objectives is to evaluate the consistency of lasmiditan 200 mg and 100 mg compared to placebo or control over **3 or 4 attacks** on the following:

- migraine headache pain relief in 2 out of 3 attacks

- migraine headache pain-freedom in 3 out of 4 attacks
- migraine headache pain relief in 3 out of 4 attacks
- consistency of lasmiditan in triptan insufficient responders

The remaining part of the secondary objectives is to evaluate the efficacy of lasmiditan 200 mg and 100 mg compared to placebo at **end of study** on the following:

- migraine-related disability measured by Migraine Disability Assessment Test (MIDAS) total score and individual items
- treatment satisfaction compared to control

## 4.3. Exploratory Objective

The exploratory objective is to assess whether lasmiditan is superior to placebo as measured by:

- efficacy in females during menses
- total migraine freedom
- consistency of 2-hour freedom from MBS during 2 out of 3 attacks
- health-related quality of life (HRQoL) with respect to domains of work functioning and energy/vitality during an acute migraine attack
- Health Care Resource Utilization (HCRU)
- efficacy of lasmiditan 50 mg
- time to meaningful relief and time to pain freedom based on patient recall time entered in the eDiary
- efficacy in patients with insufficient response to 2 or more triptans
- estimated time between attacks for each group.

Analysis details can be found in subsequent sections of this SAP.

Table LAIJ.4.1 shows the objectives and endpoints of the study.

## Table LAIJ.4.1. Objectives and Endpoints

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on migraine headache pain freedom compared to placebo | • The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack |
| • To evaluate the consistency of response to lasmiditan 200 mg and 100 mg compared to placebo | • The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 2 out of 3 attacks |
| **Secondary** | |
| *Efficacy* | |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on freedom from MBS compared to placebo | • The proportion of patients in each group that are free of MBS associated with migraine at 2 hours postdose during the first attack |
| • To evaluate the efficacy of lasmiditan 200 mg<br>• and 100 mg on pain relief compared to placebo | • The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose during the first attack. |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on sustained freedom from pain compared to placebo | • The proportion of patients in each group with 24-hour and with 48-hour sustained pain freedom during the first attack defined as pain-free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication |
| • To evaluate the need for rescue medication in patients treated with lasmiditan 200 mg and 100 mg compared to placebo | • The proportion of patients in each group requiring rescue medication for migraine within 24 hours of treatment during the first attack |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg at 2 hours on symptoms associated with migraine compared to placebo | • The proportion of patients in each group with symptoms associated with migraine at 2 hours postdose during the first attack, including each of the following: phonophobia, photophobia, nausea, vomiting |
| • To assess the probability of migraine relapse in patients treated with lasmiditan 200 mg and 100 mg compared to placebo | • The proportion of patients in each group with migraine recurrence up to 24 and 48 hours during the first attack defined as return of any headache in patients who were pain-free at 2 hours and migraine pain comes back before or at 24 hours or 48 hours. |
| • To explore the time course of lasmiditan 200 mg and 100 mg efficacy compared to placebo | • The proportion of patients in each group at each time point with pain freedom, pain relief, freedom from MBS, and no disability postdose during first attack |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on migraine-related disability compared to placebo | • Mean change from baseline in total score and individual items as measured by the MIDAS scale, in each group at end of study |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on disability during migraine attacks compared to placebo | • The proportion of patients in each group with no disability as measured by the disability item, at 2 hours postdose during the first attack |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on PGIC compared to placebo | • The proportion of patients in each group very much or much better as measured by PGIC, at 2 hours postdose during the first attack |

**Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| *Efficacy (continued)* | |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on HRQoL during an acute migraine attack compared to placebo | • Mean HRQoL score for domains of social functioning, migraine symptoms, and feelings/concerns, as measured by the 24-hour MQoLQ, in each group at 24 hours postdose during first attack |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on treatment satisfaction compared to control | • The proportion of patients in each group who are satisfied with their treatment at EOS as measured by a 4-item questionnaire |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg on health utility compared to placebo | • Mean change from baseline in utility in each group as measured by the EQ-5D-5L, at 24 hours postdose during first attack |
| • To evaluate the efficacy of lasmiditan 200 mg and 100 mg in triptan insufficient responders | • The proportions of patients in the subpopulation of triptan insufficient responders that achieve primary and secondary objectives in each group during the first attack<br>• The proportions of patients in the subpopulation of triptan insufficient responders versus other patients that achieve primary and secondary objectives in each group during the first attack |
| *Consistency* | |
| • To evaluate the consistency of lasmiditan 200 mg and 100 mg on migraine headache pain relief in 2 out of 3 attacks compared to placebo | • The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose in at least 2 out of 3 attacks |
| • To evaluate the consistency of response to lasmiditan 200 mg and 100 mg in 3 out of 4 attacks compared to control | • The proportion of patients in each group that are pain-free (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 3 out of 4 attacks |
| • To evaluate the consistency of lasmiditan 200 mg and 100 mg on migraine headache pain relief in 3 out of 4 attacks compared to control | • The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none and mild pain becoming none) in each group at 2 hours postdose in at least 3 out of 4 attacks |
| • To evaluate the consistency of lasmiditan 200 mg and 100 mg in triptan insufficient responders | • The proportions of patients in the subpopulation of triptan insufficient responders versus other patients that achieve consistency in each group defined as pain freedom during at least 2 out of 3 attacks |
| **Exploratory** | |
| • To evaluate in females the efficacy, as measured by migraine pain and associated symptoms, of lasmiditan compared to placebo on migraine attacks occurring in proximity to menses | • During a 5-day window starting 2 days before the onset of menstruation, the proportion of migraine attacks in menstruating females with migraine pain freedom, pain relief, and MBS freedom at 2 hours after dosing in each group |

**Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| **Exploratory (continued)** | |
| • To evaluate the efficacy of lasmiditan on total migraine freedom | • Proportion of patients in each group who have total migraine freedom, defined as no pain and no migraine-associated symptoms, at 2 hours postdose during the first attack |
| • To explore the effect of lasmiditan on the consistency of 2-hour freedom from MBS during 2 out of 3 attacks | • The proportion of patients in each group that are free of MBS associated with migraine at 2 hours postdose during at least 2 out of 3 attacks |
| • To evaluate the efficacy of lasmiditan on HRQoL with respect to domains of work functioning and energy/vitality during an acute migraine attack | • Mean HRQoL score for domains of work functioning and energy/vitality, as measured by the 24-hour MQoLQ, in each group at 24 hours postdose during first attack |
| • To evaluate the efficacy of lasmiditan on HCRU | • Mean change from baseline in HCRU in each group |
| • To evaluate the efficacy of lasmiditan 50 mg | • The proportions of patients with pain freedom, pain relief, MBS freedom, no disability, and very much or much better as measured by PGIC, at 2 hours postdose in patients treated with lasmiditan 50 mg during attacks 3 and 4 versus placebo during attacks 3 and 4 |
| • To explore the efficacy of lasmiditan on time to meaningful relief and the time to pain freedom | • The time to meaningful relief and time to pain freedom in each group during each attack. Date and time were entered by patients in the eDiary |
| • To evaluate the efficacy of lasmiditan in patients who insufficiently responded to 2 or more triptans | • The proportions of patients in this subpopulation that achieve primary and secondary objectives in each group during the first attack<br>• The proportions of patients in this subpopulation versus other patients that achieve the primary objective in each group during the first attack |
| • Estimated time between attacks | • Time between first and second attacks, second and third attacks, third and fourth attacks, in each group |

Abbreviations: EOS = end of study; EQ-5D-5L = EuroQol 5-dimension 5-level scale; HCRU = Health Care Resource Utilization; HRQoL = health-related quality of life; MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment Test; MQoLQ = Migraine Quality of Life Questionnaire; PGIC = patient global impression of change.

# 5. A Priori Statistical Methods

## 5.1. Study Design

Study H8H-MC-LAIJ is a prospective, multicenter, randomized, double-blind, modified parallel, placebo-controlled Phase 3 study of adult patients suffering from migraine with or without aura.

Patients will be asked to treat 4 migraine attacks with study drug on an outpatient basis.

The treatment group sequences will include 1 treatment group that receives lasmiditan 200 mg for 4 attacks, 1 treatment group that receives lasmiditan 100 mg for 4 attacks, and a control group that receives placebo for 3 attacks and lasmiditan 50 mg for 1 attack. The control group will consist of 2 treatment sequence groups (1:1) where 1 group will receive lasmiditan 50 mg for attack 3 and the other group will receive lasmiditan 50 mg for attack 4.

## 5.2. Sample Size Determination

Approximately 2100 patients will be screened to achieve approximately 1600 randomized patients, approximately 1150 patients with data for first attack, and approximately 800 patients with complete data for consistency assessment. An additional 200 patients may be randomized if there is an insufficient number of patients with complete data for consistency assessment. Patients who are randomized but not administered treatment may be replaced to ensure that at least 800 patients complete the study.

Eligible patients will be randomized in a blinded fashion in a 1:1:1 ratio to lasmiditan 200 mg, lasmiditan 100 mg, or control. The control group will consist of 2 treatment sequence groups where all patients receive placebo for 3 attacks and are randomized 1:1, where 1 group will receive lasmiditan 50 mg for attack 3 and the other group will receive lasmiditan 50 mg for attack 4.

Using a 1-sided, 2-sample comparison of proportions at a 1-sided alpha of 0.025, a sample size of 380 patients per treatment group for the first attack provides >90% power to detect a difference in headache pain-free response at 2 hours for assumed true rates of 29% for lasmiditan 100 mg and 19% for placebo for the first attack. The power is expected to be higher for the comparison of lasmiditan 200 mg to placebo given the larger effect of lasmiditan 200 mg versus lasmiditan 100 mg observed in previous studies.

For the consistency primary endpoint, assuming 0.3 and 0.2 correlation coefficients among multiple attacks for lasmiditan and placebo respectively, and assuming a consistent response rate at each attack for lasmiditan and placebo, a sample size of 260 patients per treatment group provides >90% power for 2-hour headache pain free consistency for the 200-mg dose group and nearly 90% power for consistency in the 100-mg dose group.

## 5.3. Randomization and Treatment Assignment

At Visit 2, patients will be randomly assigned treatment as described in Table LAIJ.5.1. The randomization ratio is 2:2:1:1. Country is used as stratification factor.

**Table LAIJ.5.1. Treatment Regimens**

| Regimen | Attack 1 | Attack 2 | Attack 3 | Attack 4 |
|---|---|---|---|---|
| **LTN200 mg Dose Group** | LTN200 mg<br>2×100-mg lasmiditan tablets<br>1×50 mg lasmiditan matching placebo | LTN200 mg<br>2×100-mg lasmiditan tablets<br>1×50 mg lasmiditan matching placebo | LTN200 mg<br>2×100-mg lasmiditan tablets<br>1×50 mg lasmiditan matching placebo | LTN200 mg<br>2×100-mg lasmiditan tablets<br>1×50 mg lasmiditan matching placebo |
| **LTN100 mg Dose Group** | LTN100 mg<br>1×100-mg lasmiditan tablet<br>1×50 mg lasmiditan matching placebo<br>1×100 mg lasmiditan matching placebo | LTN100 mg<br>1×100-mg lasmiditan tablet<br>1×50 mg lasmiditan matching placebo<br>1×100 mg lasmiditan matching placebo | LTN100 mg<br>1×100-mg lasmiditan tablet<br>1×50 mg lasmiditan matching placebo<br>1×100 mg lasmiditan matching placebo | LTN100 mg<br>1×100-mg lasmiditan tablet<br>1×50 mg lasmiditan matching placebo<br>1×100 mg lasmiditan matching placebo |
| **Control 1** | Placebo<br>1×50 mg lasmiditan matching placebo<br>2×100 mg lasmiditan matching placebo | Placebo<br>1×50 mg lasmiditan matching placebo<br>2×100 mg lasmiditan matching placebo | LTN50 mg<br>1×50-mg lasmiditan tablet<br>2×100 mg lasmiditan matching placebo | Placebo<br>1×50 mg lasmiditan matching placebo<br>2×100 mg lasmiditan matching placebo |
| **Control 2** | Placebo<br>1×50 mg lasmiditan matching placebo<br>2×100 mg lasmiditan matching placebo | Placebo<br>1×50 mg lasmiditan matching placebo<br>2×100 mg lasmiditan matching placebo | Placebo<br>1×50 mg lasmiditan matching placebo<br>2×100 mg lasmiditan matching placebo | LTN50 mg<br>1×50-mg lasmiditan tablet<br>2×100 mg lasmiditan matching placebo |

Abbreviations: LTN200 = lasmiditan 200 mg; LTN100 = lasmiditan 100 mg; LTN50 = lasmiditan 50 mg.

## 5.4. Endpoints

### *5.4.1.* Efficacy Endpoints

Efficacy endpoints are collected via eDiary by patient or solicited by study personnel during site visits.

#### 5.4.1.1. Patient eDiary

Patients will be introduced to the eDiary at Visit 1 and trained on the use of the eDiary at Visit 2.

Efficacy data for each attack will be collected in the eDiary. Patients will record the date and time at which their migraine headache starts. Patients will also record the date and time of taking study drug. Patients will be asked to assess their headache severity at specified time points: 0, 0.5, 1, 2, 4, 6, 24, and 48 hours postdose using the International Headache Society 4-point headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain).

In the patient eDiary, migraine pain presence, severity, and associated symptoms of migraine (nausea, phonophobia, or photophobia) and vomiting (yes/no) are assessed at scheduled time points.

The following are examples of endpoints collected or derived from data in the eDiary:

- Migraine pain-freedom
- MBS freedom
- Pain relief
- Sustained pain freedom
- Symptoms associated with migraine

Table LAIJ.5.2 shows the information collected in the eDiary during each studied migraine attack at particular time points.

**Table LAIJ.5.2. eDiary Assessments**

| **eDiary Assessment for all attacks treated with study drug** | **0h** | **0.5h** | **1h** | **2h** | **4h** | **6h** | **24h** | **48h** |
|---|---|---|---|---|---|---|---|---|
| Headache severity (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain) | X | X | X | X | X | X | X | X |
| Presence or absence (yes or no) of accompanying symptoms: photophobia, phonophobia, nausea, and vomiting | X | X | X | X | X | X | X | X |
| Select from the accompanying symptoms present (nausea, phonophobia or photophobia only) which one is the most bothersome | X | | | | | | | |
| Time at which headache relief became meaningful | | | | | X | | | |
| Time at which they become headache pain-free | | | | | X | | | |
| MQoLQ | | | | | | | X | |
| EQ-5D-5L | X | | | | | | X | |
| Disability | X | X | X | X | X | X | X | |
| PGIC | | | | X | | | X | |

Abbreviations: eDiary = electronic diary; EQ-5D-5L = EuroQol 5 Dimension 5 Level; h = hours; MQoLQ = 24-Hour Migraine Quality of Life Questionnaire; PGIC = Patient Global Impression of Change.

#### 5.4.1.2. Electronic Case Report Form

Rescue and recurrence medication is recorded by subjects in a paper journal log as part of the electronic case report form (eCRF). The information of rescue and recurrence medication will be used to derive results of efficacy endpoints.

The following questionnaires are collected during site visits and recorded in the eCRF:

- MIDAS
- HCRU

- Employment status
- Treatment satisfaction

## 5.5. Statistical Analysis

### *5.5.1. General Statistical Considerations*

Statistical analysis of this study will be the responsibility of Eli Lilly and Company (Lilly) or its designee. The SAP will be finalized and approved prior to unblinding of treatment at database lock.

Efficacy analyses will be conducted on the ITT population. This set includes all randomized patients who use at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity assessments at or before 2 hours postdose. Patients will be evaluated by the attack and group to which they were randomized.

Consistency analyses will be conducted on the ITT consistency population. This set includes all randomized patients who experienced a sufficient number of successes or failures during ITT-evaluable attacks for any of the consistency analyses. The "sufficient number" is defined differently for the 2 endpoints related to consistency (that is, 2 out of 3 attacks and 3 out of 4 attacks):

- Two of 3: To evaluate at least 2 out of 3 consistency endpoints, the results of ITT-evaluable attacks in the lasmiditan 100-mg and 200-mg groups will be assessed, and the ITT-evaluable attacks treated with placebo in the control group will be used for comparison. For patients with more than 3 ITT-evaluable attacks, only the first 3 with the same treatment will be considered.
  The population for the 2 out of 3 consistency endpoints with sufficient number of successes or failures is defined as all patients who experienced at least 2 successes or 2 failures during their first 2 or 3 ITT-evaluable attacks.
- Three of 4: To evaluate 3 out of 4 consistency endpoints; all ITT-evaluable attacks will be used. For the control group, the results of all ITT-evaluable attacks treated with lasmiditan 50 mg or placebo will be included. The control group is used for comparison. The population for 3 out of 4 consistency endpoints with sufficient number of successes or failures is defined as all patients who experienced at least 3 successes or 2 failures during ITT-evaluable attacks.

For analyses where mITT populations are specified, the definitions are the same as for ITT populations, except based on mITT-evaluable attacks. For details about the analysis populations, see Section 5.5.1.5.

Tests of the primary and gated secondary endpoints will be conducted using a multiple comparisons procedure that preserves overall type I error at 1-sided alpha level of 0.025.

Tests of all other safety and efficacy endpoints will be conducted at a 2-sided significance level of 0.05.

Continuous variables will be generally summarized using descriptive statistics (that is, n [number of subjects with available data], mean, median, standard deviation, minimum, and maximum).

Minimum and maximum values will be presented to the same precision as the raw data. Mean nd median will be presented to 1 more decimal place than the raw data. Standard deviation will be presented to 2 more decimal places than the raw data. P-values will be presented to 3 decimal places.

Categorical variables will be summarized using counts and percentages. Unless otherwise specified, percentages will be calculated using the numbers of subjects in the summarized population in each treatment group as denominators. Percentages will be presented with a precision of 1 digit after the decimal.

For safety analyses the scheduled Visit 1 or Visit 2 will be used for baseline. For efficacy analyses, values in the eDiary at time of dosing will be used for baseline. For efficacy measures not collected in the eDiary, such as MIDAS, the scheduled Visit 1 or Visit 2 will be used for baseline.

The statistical evaluation will be performed using SAS version 9.4 or higher.

#### 5.5.1.1. Adjusting of Covariates

The randomization is stratified by country. Region (North America, Europe, and Asia) will be included in all statistical models.

#### 5.5.1.2. Handling of Missing Values

For efficacy analysis, if a patient is either ITT or mITT evaluable (defined in Section 5.5.1), the patient is included in the corresponding analysis.

Subjects who fail to record information at a particular analysis time point will have that value considered missing in the respective table, unless otherwise specified.

1. A patient was considered a non-responder for both pain freedom and pain relief at a specific time point if the patient had an evaluable attack and did not provide a pain severity rating at the specific time point.
2. A patient was considered a non-responder for MBS freedom at a specific time point if the patient had an evaluable attack and defined MBS at baseline and did not provide a symptom rating at the specified time point.
3. A patient was considered a non-responder for pain freedom, pain relief, and MBS freedom at a specific time point if the patient had an evaluable attack and took any rescue medication at or before the specific time point.

Based on these rules, a patient can only achieve success for an endpoint (for example, pain freedom, pain relief, or MBS freedom) at a specified time point if the patient has an

evaluable attack and non-missing data at the specific time point and has not taken any migraine medication at or prior to that specific time point.

The missing values are assumed as failures because only the proportion of successes are reported out of the total number of evaluable patients. Other analyses will use observed data and will apply no imputation for missing data.

A sensitivity analysis for missing data under alternative assumptions will be performed as described in Section 5.5.13.

#### 5.5.1.3. Multicenter Studies

Region will be included in the model as a factor.

#### 5.5.1.4. Multiple Comparisons/Multiplicity

In order to control for overall type I error, the primary and gated secondary analyses will be tested using a multiple comparisons procedure that preserves overall type I error at a 1-sided alpha level of 0.025.

The primary objective is to assess the efficacy of lasmiditan 200 mg and lasmiditan 100 mg on migraine headache pain freedom. The primary endpoint is the proportion of patients having pain freedom at 2 hours post-dose during the first attack. This analysis will compare each dose of lasmiditan with placebo. The coprimary objective is to assess the consistency of efficacy of lasmiditan 200 mg and lasmiditan 100 mg. This endpoint is defined as the proportion of patients having pain freedom at 2 hours post-dose in at least 2 out of 3 attacks. This analysis will compare each dose of lasmiditan with placebo.

Table LAIJ.5.3 shows the hypotheses in the multiple testing scheme.

**Table LAIJ.5.3. Hypothesis in Multiple Testing Scheme**

| Hypothesis | Description |
|---|---|
| H1 | Lasmiditan 100 mg vs. placebo on 2-hour pain freedom in the first attack |
| H2 | Lasmiditan 100 mg vs. placebo on consistency of 2 hour-pain freedom in 2 out of 3 attacks |
| H3 | Lasmiditan 100 mg vs. placebo on 2-hour pain relief in the first attack |
| H4 | Lasmiditan 100 mg vs. placebo on consistency of 2-hour pain relief in 2 out of 3 attacks |
| H5 | Lasmiditan 100 mg vs. placebo on 1-hour pain relief in the first attack |
| H6 | Lasmiditan 100 mg vs. placebo on 24-hour sustained pain freedom in the first attack |
| H7 | Lasmiditan 100 mg vs. placebo on 2-hour pain freedom in triptan insufficient responders (TIR) in the first attack |
| H8 | Lasmiditan 100 mg vs. placebo on 2-hour no disability in the first attack |
| H9 | Lasmiditan 200 mg vs. placebo on 2-hour pain freedom in the first attack |
| H10 | Lasmiditan 200 mg vs. placebo on consistency of 2-hour pain freedom in 2 out of 3 attacks |
| H11 | Lasmiditan 200 mg vs. placebo on 2-hour pain relief in the first attack |
| H12 | Lasmiditan 200 mg vs. placebo on consistency of 2-hour pain relief in 2 out of 3 attacks |
| H13 | Lasmiditan 200 mg vs. placebo on 1-hour pain relief in the first attack |
| H14 | Lasmiditan 200 mg vs. placebo on 24-hour sustained pain freedom in the first attack |

**Hypothesis in Multiple Testing Scheme**

| | |
|---|---|
| H15 | Lasmiditan 200 mg vs. placebo on 48-hour sustained pain freedom in the first attack |
| H16 | Lasmiditan 200 mg vs. placebo on 1-hour pain freedom in the first attack |
| H17 | Lasmiditan 200 mg vs. placebo on 2-hour pain freedom in triptan insufficient responders (TIR) in the first attack |
| H18 | Lasmiditan 200 mg vs. placebo on 2-hour no disability in the first attack |

A graphical Multiple Comparisons Procedure (gMCP; Bretz, 2009) will be used to control overall type I error. Initial alphas specified are assigned to hypotheses comparing pain freedom at 2 hours in the first attack for each dose of lasmiditan versus placebo. For each dose, if the hypothesis of pain freedom has been rejected, then the test comparing lasmiditan with placebo on consistency of efficacy will be conducted. If a subsequent test is rejected, then the alpha for that test will be propagated to the other hypotheses as specified in the scheme. Any nonrejected hypotheses may be retested using the algorithm specified in gMCP. The overall family-wise type I error rate is controlled at 0.025 one-sided level in the strong sense. The planned testing order and alpha sharing is shown in Figure LAIJ. 5.1.

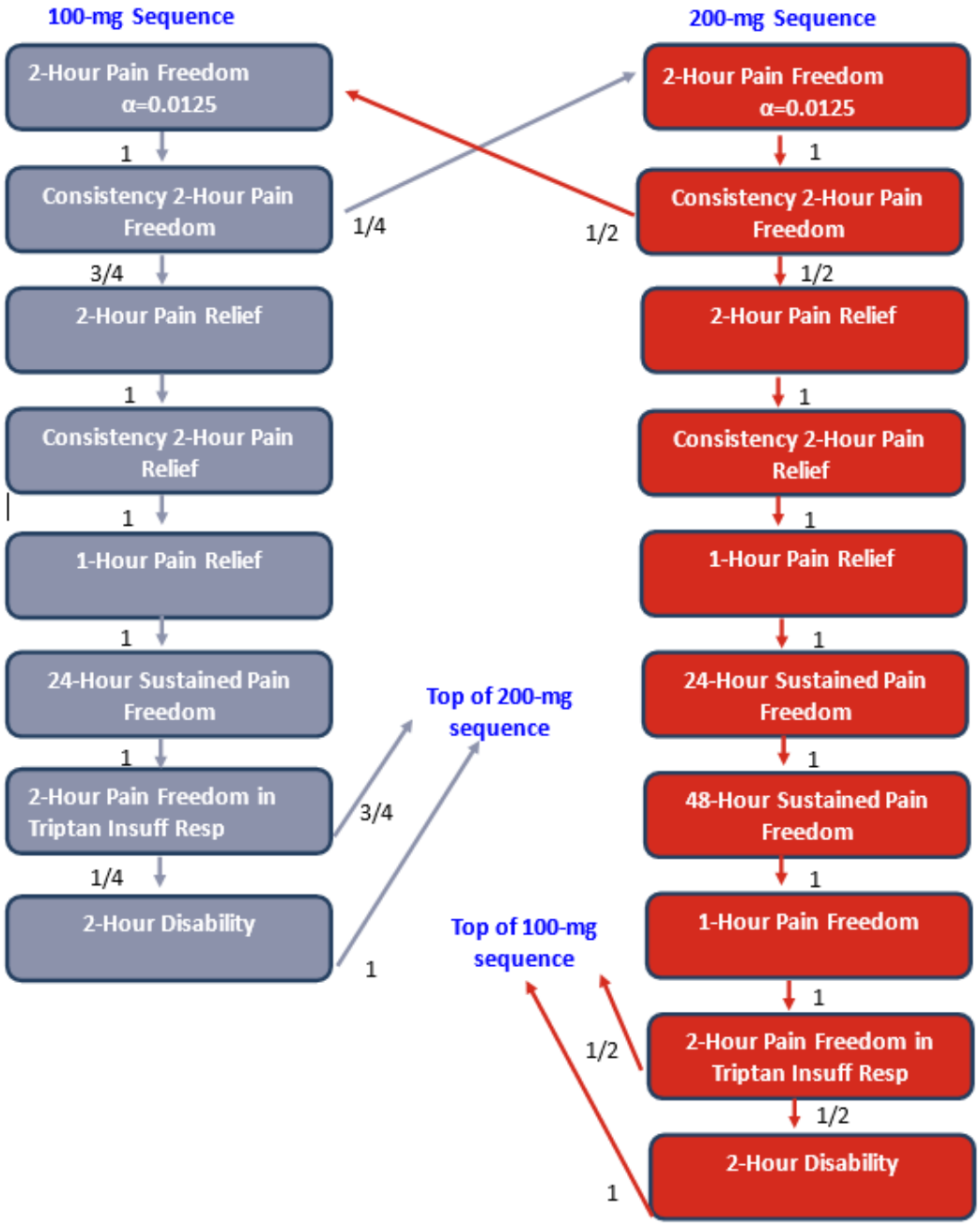


**Figure LAIJ. 5.1. Graphical Representation of Multiple Testing Procedure**

Within this gMCP procedure, all 18 hypothesis (H1-H18) will be tested leveraging the ITT or ITT consistency populations as defined in the following section.

Sensitivity analysis on primary and gated secondary endpoints within the mITT and mITT consistency populations will also be performed without adjustment for multiplicity (defined in Section 5.5.1.5).

#### 5.5.1.5. Analysis Populations

For purposes of analysis, the populations are defined in Table LAIJ.5.4. For efficacy analyses, patients will be evaluated by attack and by the group to which they are randomized. For safety analyses, patients will be analyzed according to the treatment they actually received, which will generally be the same as randomized treatment unless there is an error.

**Table LAIJ.5.4. Analysis Populations**

| Population | Description |
|---|---|
| Entered | All participants who sign informed consent |
| ITT | All randomized patients who use at least 1 dose of study drug for an ITT-evaluable attack, defined as a treated attack of at least mild pain severity with any postdose pain severity assessments at or before 2 hours postdose. |
| mITT | All randomized patients who use at least 1 dose of study drug for an mITT-evaluable attack, defined as a treated attack of at least moderate pain severity with any postdose pain severity assessments at or before 2 hours postdose. |
| ITT consistency | All randomized patients who experience a sufficient number of successes or failures (defined in Section 5.5.1) during ITT-evaluable attacks for any of the consistency analyses. |
| mITT consistency | All randomized patients who experience a sufficient number of successes or failures (defined in Section 5.5.1) during mITT-evaluable attacks for any of the consistency analyses. |
| Safety | All randomized patients who take at least 1 dose of study drug, regardless of whether or not they undergo any study assessments. |

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat.

#### 5.5.1.6. Treatment Groups

The treatment groups are summarized in Table LAIJ.5.1 and will include 1 treatment group that receives lasmiditan 200 mg for 4 attacks, 1 treatment group that receives lasmiditan 100 mg for 4 attacks, and a control group that receives placebo for 3 attacks and lasmiditan 50 mg for 1 attack. The control group will consist of 2 treatment sequence groups (1:1), where 1 group will receive lasmiditan for attack 3 and the other group will receive lasmiditan for attack 4. The placebo group will consist of the placebo part in the control group. The lasmiditan 50-mg group will consist of the lasmiditan 50 mg treated attack in patients randomized to the control group.

### *5.5.2. Health Outcomes Questionnaires*

The following questionnaires are collected in the study.

- MIDAS
- HRQoL

- Migraine Treatment Optimization Questionnaire (mTOQ) 6 scores
- EQ-5D-5L
- Treatment satisfaction

Details on analyses of health outcomes measures can be found in Section 5.5.9.

### *5.5.3. eDiary Assessment Times for Efficacy and Exploratory Analysis*

There will be some scenarios when responses appear to have been limited by the eDiary programming if questions are not answered in the expected order or during the programmed window.

Some specific scenarios are listed below for derivation of analysis time points for efficacy and exploratory endpoints.

1. Missing dose dates and times: If a dose is reported as being taken in the eCRF, that is not entered into the eDiary (either due to not being allowed to enter because of eDiary programming issues or just failing to enter data), then the data for this dose will not be included in any of the efficacy analyses as no reliable efficacy data are available. However, this information will be used to 1) determine specific treatment per attack for the control group, and 2) include patients in the safety population.
2. Baseline assessment: In the eDiary, retrospective reporting of baseline migraine severity is allowed, however, the baseline severity must be at least mild to be included in the primary analyses.

### *5.5.4. Patient Disposition*

Study and treatment disposition will be summarized overall and by treatment group (that is, lasmiditan 200 mg, lasmiditan 100 mg, control group combined). Reasons for discontinuation for all patients will be tabulated for treatment groups.

The following will be summarized overall and by treatment group as counts and percentages for all randomized patients:

- Treated
- Not treated

For treated patients, the number of treated attacks will be displayed.

The following will be summarized overall and by treatment group for randomized and safety population:

- Subjects who completed the study

- Randomized subjects at each investigative site
- Reasons subjects discontinued:
    - Adverse Event
    - Death
    - Withdrawal by subject
        - Concern about study procedures/perceived risks
        - Scheduling conflicts
        - Subject is moving or has moved
        - Personal issue unrelated to trial
        - Other
    - Physician decision
    - Non-compliance with study drug
    - Protocol deviation
    - Study terminated by Institutional Review Board/Ethics Review Board
    - Lost to follow-up
    - Study terminated by Sponsor
    - Lack of efficacy
    - Pregnancy
    - Other

The number and percentage of subjects in each disposition category will be presented; percentages will be based on the number of all subjects within the corresponding population.

Disposition data and all subjects who discontinue from the study will be presented in a separate listing.

A listing will be provided for subjects with treatment unblinded by site if this happened during the trial.

Patient allocation by investigator will be summarized for all ITT patients.

### *5.5.5. Important Protocol Deviations*

Important protocol deviations that potentially compromise the data integrity and patients' safety will be summarized by treatment group/sequence for all randomized patients. Analysis will be

conducted for primary endpoints on per protocol population defined as patients who have completed the study without the protocol deviations as described in Section 6.

A listing of important protocol deviations for all randomized patients will be provided in the clinical study report (CSR).

Those protocol deviations related to COVID-19 will be indicated as such in the CSR.

### *5.5.6. Patient Characteristics*

Patient characteristics will be summarized by treatment group and overall. Summaries will include descriptive statistics for continuous measures and for categorical measures (sample size, frequency, and percentages).

Patient characteristics will be summarized for ITT, mITT, and safety populations.

- Demographics (age, sex, race, ethnicity, height, weight, and body mass index)
    - If multiple races are selected in the CRF, the patient will be classified as multiple race
    - Ethnicity will be reported for countries where such reporting is allowed
- Migraine history
    - Duration of migraine
    - Average migraines/month in past three months
- MIDAS at baseline (see Section 5.5.6.1)
    - MIDAS total scores
    - MIDAS categorical grades (Grade I/II, Grade III, Grade IV-A, and Grade IV-B)
    - Number of days with headaches in the past 3 months
    - Average headache pain in past 3 months
- Experienced migraine
    - with aura
    - without aura
    - with and without aura
- Triptan experience (experienced or naive)
- Summarize number of current/prior triptans per patient, mean (range)
- Summarize triptan insufficient responders using each of the following definitions:
    - Overall response none/poor (based on most recent triptan, [either ongoing start date <= **V1** and ongoing on CM1001 or if no ongoing triptan, most recent from CM4001])
    - Inconsistent response (based on most recent triptan, [either ongoing start date <= **V1** and ongoing on CM1001 or if no ongoing triptan, most recent from CM4001])
    - Triptan discontinuer (based only on CM4001 IF no ongoing triptan on CM1001)
    - mTOQ poor or very poor response (based only on ongoing most recent triptan – see definition in Section 5.5.11). mTOQ scores will be based on the answers to 4 questions.

  - Composite triptan insufficient responder (composite of inconsistent response, triptan discontinuer, mTOQ poor or very poor response).
- Triptan Contraindicated based on medical history (definition can be found in Section 5.5.11).

Age (years) will be calculated as (informed consent date – imputed date of birth + 1)/365.25. Average days in a year = 365.25, reflecting the Julian Year of 3 years with 365 days each and 1 leap year of 366 days. Birth month and day are imputed to be 01 July if only birth year is collected in the eCRF.

Duration of migraine history, presented in years, will be calculated as (informed consent date - date of migraine diagnosis + 1)/365.25.

All demographic data will be presented in a listing.

#### 5.5.6.1. MIDAS at Baseline

Migraine Disability Assessment Test total scores, number of days with headaches over the past 3 months, and average headache pain severity over the past 3 months will be summarized by treatment group/sequence as described above.

The MIDAS is a 5-item questionnaire; the MIDAS total score is calculated as the sum of the answers to all 5 questions.

Average pain is measured on a scale from 0 to 10, where 0 is no pain at all and 10 is pain as bad as it can be.

In addition to the continuous analysis of MIDAS total scores, a categorical analysis will also be performed based on MIDAS categorical grades: Grade I/II, Grade III, Grade IV-A, and Grade IV-B. For clinical interpretability, 4 categorical grades were developed based on the total score: Grade I (0 to 5) is for little or no disability, Grade II (6 to 10) is for mild disability, Grade III (11 to 20) is for moderate disability, and Grade IV (21+) is for severe disability. The severe disability category has subsequently been subdivided into Grade IV-A (severe [21 to 40]) and Grade IV-B (very severe [41 to 270]).

Answers to individual MIDAS questions will be presented in a listing.

#### 5.5.6.2. Pre-Existing Conditions and Medical History

Medical history and pre-existing conditions will be summarized by treatment group for the safety population. Medical history and pre-existing conditions will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), and sorted alphabetically by system organ class (SOC) and then preferred term (PT) by frequency. Subjects with multiple occurrences of the same medical history term will be counted once within the corresponding SOC and PT. All medical history will be presented in a listing.

### 5.5.7. Prior Triptan Therapy

The proportion of patients who received prior triptan therapy will be summarized using anatomical therapeutic chemical (ATC) level 3 class and World Health Organization (WHO) drug name by treatment group/sequence for the safety population.

The responses to prior triptans, and the discontinuation reasons are used to define the triptan insufficient response subgroup; this information will be presented in a patient triptan experience table.

### 5.5.8. Concomitant Therapy

The frequency and percentage of all concomitant medications use will be presented by treatment group and summarized for the safety population using ATC level 2 class and WHO drug name. Medications will be coded using the latest version of the WHO Drug Dictionary and sorted by frequency of preferred name.

The proportion of patients who received concomitant medication collected from eCRF will be summarized for patients in the safety population.

All concomitant medication data will be presented in a listing.

### 5.5.9. Efficacy Analyses

Table LAIJ.5.5 lists the major efficacy analyses. The first attack data is used to assess efficacy objectives. Three or 4 attacks data are used to assess consistency objectives.

**Table LAIJ.5.5. Primary, Gated Secondary, and Other Secondary Efficacy Variables and Analysis Methods**

| Subcategory | Type | Table Name | Population | Time Frame | Analysis | Attack(s) |
|---|---|---|---|---|---|---|
| Pain-Free | Table | Summary of Headache Pain Free - ITT Population* | ITT | 2h | LOGISTIC | 1st |
| Pain-Free | Table | Summary of Headache Pain Free - ITT Population** | ITT | 1h | LOGISTIC | 1st |
| Pain-Free | Table | Summary of Headache Pain Free - mITT Population | mITT | 1h,2h | LOGISTIC | 1st |
| Pain-Free | Table | Summary of Headache Pain Free at 2 hours in 2 out of 3 Treated Migraines -ITT -Consistency* | ITT-Consistency | 2h | LOGISTIC | All 4 |
| Pain-Free | Table | Summary of Headache Pain Free at 2 hours in 3 out of 4 Treated Migraines -ITT -Consistency | ITT-Consistency | 2h | LOGISTIC | All 4 |
| Pain-Free | Table | Time to Headache Pain-Free Through 24 Hours Post-Dose - ITT Population | ITT | up to 24h | KM | 1st |
| Pain-Free | Figure | Time to Headache Pain-Free Through 24 Hours Post-Dose - mITT Population | mITT | up to 24h | KM | 1st |
| Sustained Pain-Free | Table | Summary of Sustained Pain Freedom - ITT Population ** | ITT | 24h, 48h | LOGISTIC | 1st |
| Sustained Pain-Free | Table | Summary of Sustained Pain Freedom - mITT Population | mITT | 24h, 48h | LOGISTIC | 1st |
| Rescue medication | Table | Summary of Rescue Medication Taken by Patients- ITT Population | ITT | 0-2h; 2h-24h;24h-48h | LOGISTIC | 1st |
| Pain-Relief | Table | Summary of Headache Pain - Relief - ITT Population ** | ITT | 1h, 2h | LOGISTIC | 1st |
| Pain-Relief | Table | Summary of Headache Pain - Relief - mITT Population | mITT | 1h, 2h | LOGISTIC | 1st |
| Pain-Relief | Table | Summary of Headache Pain Relief at 2 Hours in 2 out of 3 Migraines –ITT Consistency** | ITT-Consistency | 2h | LOGISTIC | All 4 |
| Pain-Relief | Table | Summary of Headache Pain Relief at 2 Hours in 3 out of 4 Migraines –ITT Consistency | ITT-Consistency | 2h | LOGISTIC | All 4 |
| Pain-Relief | Table | Time to Headache Pain-Relief Through 24 Hours Post-Dose - ITT Population | ITT | up to 24h | KM | 1st |
| Pain-Relief | Figure | Time to Headache Pain-Relief Through 24 Hours Post-Dose - mITT Population | mITT | up to 24h | KM | 1st |

**Primary, Gated Secondary, and Other Secondary Efficacy Variables and Analysis Methods**

| Subcategory | Type | Table Name | Population | Time Frame | Analysis | Attack(s) |
|---|---|---|---|---|---|---|
| MBS | Table | Summary of Free of Most Bothersome Symptom - ITT Population | ITT | 2h | LOGISTIC | 1st |
| MBS | Table | Summary of Free of Most Bothersome Symptom -mITT Population | mITT | 2h | LOGISTIC | 1st |
| Pain-Free | Table | Summary of Headache Pain Free – Triptan Insufficient responder Subpopulation** | ITT | 2h | LOGISTIC | 1st |
| Pain-Free | Table | Summary of Headache Pain Free – Triptan Insufficient responder Subpopulation | mITT | 2h | LOGISTIC | 1st |
| Pain-Free | Table | Summary of Headache Pain Free at 2 hours in 2 out of 3 Treated Migraines - Triptan Insufficient responder Subpopulation | ITT-Consistency | 2h | LOGISTIC | All 4 |
| Migraine Recurrence | Table | Summary of Recurrence of Migraine- ITT Population | ITT | 2h-24h;24h-48h | LOGISTIC | 1st |
| MBS | Table | Summary of Most Bothersome Symptom by Chosen Symptom - ITT Population | ITT | 2h | LOGISTIC | 1st |
| Migraine Symptom | Table | Summary of Migraine Symptoms Present at Assessment Times - ITT Population | ITT | up to 24h | LOGISTIC | 1st |
| MBS | Figure | Time to Most Bothersome Symptom-Free Through 24 Hours Post-Dose - ITT Population | ITT | up to 24h | KM | 1st |
| MBS | Figure | Time to Most Bothersome Symptom-Free Through 24 Hours Post-Dose -mITT Population | mITT | up to 24h | KM | 1st |
| MIDAS | Table | Summary of Mean Change from Baseline in Total Score and Individual Items as Measured by the MIDAS Scale - ITT Population | ITT | EOS | ANCOVA | After 4th |
| Disability | Table | Summary of Proportion of Patients in Each Group with No Disability as Measured by the Disability Item, at 2 hours Post Dose during the First Attack - ITT Population ** | ITT | 2h | LOGISTIC | 1st |

**Primary, Gated Secondary, and Other Secondary Efficacy Variables and Analysis Methods Subcategory**

| Subcategory | Type | Table Name | Population | Time Frame | Analysis | Attack(s) |
|---|---|---|---|---|---|---|
| Disability | Table | Summary of Proportion of Patients in Each Group with No Disability as Measured by the Disability Item, at 2 Hours Post Dose during the First Attack -mITT Population | mITT | 2h | LOGISTIC | 1st |
| PGIC | Table | Summary of Proportion of Very Much or Much Better in Patient Global Impression of Change - ITT Population | ITT | 2h | LOGISTIC | 1st |
| PGIC | Table | Summary of Proportion of Very Much or Much Better in Patient Global Impression of Change - mITT Population | mITT | 2h | LOGISTIC | 1st |
| HRQoL | Table | Summary of Mean HRQoL Score for Domains of Social Functioning, Migraine Symptoms, and Feelings/Concerns, as Measured by the 24-hour MQoLQ- ITT Population | ITT | 24h | ANCOVA | 1st |
| Satisfaction | Table | Summary of Proportion of Patients in Each Group Who Are Satisfied with their Treatment at EoS as Measured by a 4-item Questionnaire - ITT Population | ITT | EOS | LOGISTIC | After all treated |
| EQ-5D-5L | Table | Summary of Mean Change from Baseline in Utility in Each Group as Measured by the EQ-5D-5L- ITT Population | ITT | 24h | ANCOVA | 1st |

Abbreviations: ANCOVA = analysis of covariance; EoS = end of study; EQ-5D-5L = EuroQol 5-dimension 5-level scale; h = hour; HRQoL = Health-Related Quality of Life; KM = Kaplan-Meier; MBS = most bothersome symptom; MIDAS = Migraine Disability Assessment Test; MQoLQ = Migraine Quality of Life Questionnaire; PGIC = Patient Global Impression of Change.

* Primary Analyses

** Gated Secondary Analyses

The definitions of analysis and response variables are listed as follows:

**Patient Migraine Pain Freedom**

The proportion of patients in each group that are free of migraine pain at 2 hours postdose during the first attack will be summarized.

**MBS freedom**

Most bothersome symptom freedom is defined as the absence of the associated symptom of migraine (nausea, phonophobia, or photophobia) at the indicated assessment time that was identified at baseline as the most bothersome symptom. Subjects who record that no symptoms were present at time of dose are excluded from the MBS analysis. At the indicated assessment time, a subject is not counted as being MBS-free if he or she used rescue medication at or before those times.

If a patient reported more than one symptom and did not specify the most bothersome, then all recorded symptoms are considered as MBS, and to successfully achieve MBS at a postdose time point, all of the recorded symptoms at baseline must be absent.

The proportion of patients in each group that are free of MBS associated with migraine at 2 hours postdose during the first attack will be summarized along with the MBS selected.

**Pain relief**

Pain relief is defined as moderate or severe headache pain becoming mild or none and mild pain becoming none.

The proportion of patients with pain relief in each group at 2 hours postdose during the first attack will be summarized.

**Sustained pain freedom**

Sustained pain freedom is defined as pain-free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication.

The proportion of patients in each group with 24-hour and with 48-hour sustained pain freedom during the first attack will be summarized.

**Need of rescue medication**

Patients should not take any medications until 2 hours after taking a dose of study drug and completing the 2-hour assessments. After that, they may take excluded alternative medications for rescue or recurrence.

Response variable is the proportion of patients in each group requiring rescue medication for migraine within 24 hours of treatment during the first attack.

**Symptoms associated with migraine**

Response variable is the proportion of patients in each group with symptoms associated with migraine at 2 hours postdose during the first attack, including each of the following: phonophobia, photophobia, nausea, and vomiting.

**Patient global impression of change**

Patient global impression of change will be measured at 2 and 24 hours postdose with a 7-point scale ranging from very much better to very much worse during each migraine.

The distribution of responses and the proportion of patients in each group having very much or much better response in PGIC, at 2 and 24 hours postdose during the first attack will be summarized.

**Disability**

Disability is measured on a 4-point scale: not at all (0); mild interference (1); marked interference (2); need complete bed rest (3). Distribution of responses (no, mild, marked, and complete) and proportion of patients with score = 0 for each group at each post baseline time point is analyzed. Note that patients with 0 severity at baseline will be excluded from the analysis.

The proportion of patients in each group with no disability at 2 hours postdose during the first attack will be summarized.

Shift table analysis will be performed for each postdose time points. Frequency and percentages will be calculated for the combinations of baseline and post baseline assessment results.

**MIDAS**

The MIDAS is a patient-rated scale which was designed to quantify headache-related disability over a 3-month period. This instrument consists of 5 items that reflect the number of days reported as missed, or with reduced productivity at work or home and social events. Each question is answered as the number of days during the past 3 months of assessment, ranging from 0 to 90, with the total score being the summation of the 5 numeric responses.
MIDAS is collected at baseline with a recall period of "in the past 3 months" and again at end of study with a recall period of "since last visit." The change from baseline in total score, number of days with headache, and average headache pain will be analyzed. In order to avoid an overlap in recall period at end of study, a weighted score will be calculated based on the length of time a patient has been enrolled in the study for total score and headache days (but not for severity) using the following formula:

Weighted MIDAS score= raw score x 90 days/days since baseline assessment

**HRQoL** (24-hour MQoLQ)

There are 5 domains in the 24-hour MQoLQ, which are defined as follows.

- Work functioning domain items: (1) ability to do normal everyday work, (2) ability to operate machinery or a motor vehicle, and (3) ability to stay alert.
- Social functioning domain items: (1) interactions with people who are close to you, (2) interactions with other people, and (3) ability to enjoy life.
- Energy/vitality domain items: (1) energy level, (2) ability to have a good night's sleep, and (3) mood.
- Migraine symptoms domain items: (1) have throbbing head pain, (2) have increased sensitivity to light and/or noise, and (3) have nausea.
- Feelings/concerns domain items: (1) feel upset about having migraine headaches, (2) feel physically uncomfortable, and (3) feel concern that your migraine medication wouldn't relieve your migraine headache symptoms.

Each domain will be analyzed separately. Each domain consists of 3 questions answered on a 7-point scale, where 1 indicates maximum impairment and 7 indicates no impairment. A domain score is calculated by summing the responses to the 3 questions and the domain score ranges from 3 to 21. The response variable in this analysis is raw values at 24 hours.

Mean 24-hour MQoLQ score for all 5 domains will be calculated for each group at 24 hours postdose during first attack.

**EQ-5D-5L**

The EQ-5D-5L is assessed at Visit 2 and during each individual attack at baseline and at 24 hours postdose. During the migraine attack, the eDiary is programmed such that the subject is prompted to answer the EQ-5D-5L questionnaire after date/time of dosing is entered/saved. Since the recall period is "today," the first collection of EQ-5D-5L during the attack will be considered as baseline.

Mean change from baseline in utility score using UK value set and visual analog scale score will be calculated for each group at 24 hours postdose during the first attack.

**Satisfaction of treatment**

There are 4 questions. Each question will be analyzed separately at end of study:

- If the patient would recommend this treatment to another patient (ranging from strongly disagree to strongly agree). Response variable is proportion of patients in each group: Distribution of responses and proportion of patients with agree or strongly agree will be summarized for each treatment group.
- The patient's willingness to take this treatment again (ranging from strongly disagree to strongly agree). Response variable is proportion of patients in each group: Distribution of responses and proportion of patients with agree or strongly agree will be summarized for each treatment group.

- The patient's level of satisfaction (ranging from extremely dissatisfied to extremely satisfied). Response variable is proportion of patients in each group: Distribution of responses and proportion of patients with very satisfied or extremely satisfied will be summarized for each treatment group.
- The patient's preference when comparing this treatment to the previous treatment ("prefer this treatment in comparison to my previous treatment" to "prefer my previous treatment in comparison to this treatment"). Response variable is proportion of patients in each group: Distribution of responses and proportion of patients with who prefer this treatment in comparison to their previous treatment will be summarized for each treatment group.

**Health Care Resource Utilization and Employment Status**

Health Care Resource Utilization will be solicited by study personnel while documenting patient responses. The HCRU consists of 3 questions, asking about the number of hospital emergency room visits, overnight stays in a hospital, and any other visits with a healthcare professional that occurred since the patient started in the study, outside of visits associated with their participation in the clinical trial. Patients are also specifically asked about the number of healthcare events that are related to migraine attacks. The baseline visit will include the same questions but with the past 6 months as the recall period.

Health Care Resource Utilization data will be summarized by treatment group as follows: for all-cause visits and for migraine specified visits, percentage of patients with at least 1 hospital visit will be calculated along with the distributions.

Employment status will be summarized by treatment group. Data will include both baseline and end of study.

#### 5.5.9.1. Primary Outcome and Methodology

The first primary objective of this study is to assess the efficacy of lasmiditan 200 mg and lasmiditan 100 mg on migraine headache pain freedom. The primary measurement is the proportion of patients having pain freedom (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose during the first attack. This analysis will be performed on the ITT population.

The second primary objective of this study is to assess the consistency of efficacy of lasmiditan 200 mg and lasmiditan 100 mg on migraine headache pain freedom. The primary measurement is the proportion of patients having pain freedom (defined as mild, moderate, or severe headache pain becoming none) at 2 hours postdose in at least 2 out of 3 attacks. This analysis will be performed using the ITT consistency population.

Logistic regression with categorical terms for treatment and geographic region will be used to statistically evaluate the proportions of patients achieving migraine headache pain freedom in first attack for lasmiditan treatment groups versus placebo and also in the consistency analyses comparing lasmiditan treatment groups versus placebo. In order to control for overall type I

error, the primary analyses will be tested using a multiple comparisons procedure (see Section 5.5.1.4 for details).

A sample SAS code for logistic regression is the following:

```
PROC LOGISTIC DATA = ADEF;
CLASS TRT(REF="PL") Region/ PARAM=REF;
MODEL RESP(EVENT='1')= TRT Region ;
RUN;
```

#### 5.5.9.2. Gated Secondary Analyses

The gated secondary measures will be analyzed using the ITT and ITT consistency populations.

In order to control for overall type I error, the gated secondary analyses will be tested using a multiple comparisons procedure (see Section 5.5.1.4 for details).

#### 5.5.9.3. Additional Secondary and Exploratory Efficacy Analyses

Additional secondary and exploratory measures will be analyzed using the ITT and ITT consistency populations. Additional analyses of mITT and mITT consistency populations will be conducted. No adjustment for multiplicity is implemented.

Logistic regression will be used to statistically evaluate the proportions among lasmiditan groups and the placebo group for other secondary endpoints.

Analysis of variance or analysis of covariance (ANCOVA) will be used to assess the effect of lasmiditan over placebo or control for continuous endpoints. The model includes fixed categorical effect of treatment and geographic region and baseline as covariate.

For analyses representing relatively small sample sizes, if the model described in Section 5.5.9.1 does not converge for logistic regression analyses, then the Firth option will be used in the model.

### *5.5.10. Safety Analyses*

The safety and tolerability of treatment will be assessed by summarizing the following:

- Treatment-emergent adverse events (TEAEs)
  - By PT by decreasing frequency
  - By SOC
  - By maximum severity
  - By relationship to investigational product as assessed by investigator
- Other adverse events (AEs)
- Serious adverse events (SAEs)
- Treatment-emergent serious adverse events (TEAE SAEs)
- AEs leading to discontinuation
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Vital signs and weight

- Laboratory measurements
- Driving accidents/violations

All safety analyses will be performed with the Safety population. Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits.

#### 5.5.10.1. Adverse Events

Adverse events will be coded by the MedDRA latest version.

In an overview table, the number and percentage of subjects who reported an AE, TEAE, or SAE, who died, or who discontinued due to an AE or TEAE will be summarized by treatment group.

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

#### 5.5.10.2. Treatment-Emergent Adverse Events

For each TEAE, the severity level of the event (mild, moderate, or severe) will be recorded. The MedDRA lowest level term (LLT) will be used in the treatment-emergent computation. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT or SOC) will be the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

An AE with time of onset within 48 hours after a dose of study drug, or an event that worsens in intensity within 48 hours after a dose of study drug, will be considered a TEAE. An AE that occurs outside of 48 hours after any dose of study drug will not be considered a TEAE.

Events with a missing severity at baseline will be treated as "mild" in severity. Adverse events that are missing severity after baseline will be considered treatment-emergent if they occurred within the time period for considering an AE as a TEAE.

Missing AE start date/time and end date/time will be imputed by the rules shown in Table LAIJ.5.6. After imputation, if the AE start date is still missing, the AE will be assumed to be treatment-emergent to first attack, unless the AE end date/time is before the dosing date/time.

**Table LAIJ.5.6. Rules of Imputation of Date and Time Related to Adverse Events**

| START DATE/TIME | STOP DATE/TIME | ACTION |
|---|---|---|
| Known | Known /Partial /Missing | If start date/time < dose date/time, then not TEAE.<br><br>If start date/time ≥ dose date/time and < (dose date/time + 48 hours [or 2 days]), then TEAE. |
| | | |
| Partial, but known components show that it cannot be on or within 48 hours after dose date/time | Known /Partial /Missing | Not TEAE. |
| | | |

**Rules of Imputation of Date and Time Related to Adverse Events**

| | | |
|---|---|---|
| Partial, could be on or within 48 hours after dose date/time | Known | If stop date/time < dose date/time, then not TEAE.<br><br>If stop date/time ≥ dose date/time, then TEAE. |
| | Partial | Impute stop date/time as latest possible date/time (for example last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date/time < dose date/time, then not TEAE.<br><br>If stop date/time ≥ dose date/time, then TEAE. |
| | Missing | Assumed TEAE. |
| Missing | Known | If stop date/time < 1st dose date/time, then not TEAE.<br><br>If stop date/time ≥ 1st dose date/time, then TEAE for 1st attack. |
| | Partial | Impute stop date/time as latest possible date/time (for example, last day of month if day unknown or 31st December if day and month are unknown), then:<br><br>If stop date/time <1st dose date/time, then not TEAE.<br><br>If stop date/time ≥ 1st dose date/time, then TEAE for 1st attack. |
| | Missing | Assumed TEAE for 1st attack. |

Abbreviation: TEAE = treatment-emergent adverse event.

Frequency counts and percentages will be presented for subjects with TEAEs within each SOC and PT, separated by treatment group. Both subjects experiencing any event and total events will be presented. Descriptive statistics will also be calculated for each treatment group for TEAE relationship and TEAE severity. If multiple intensities are reported for a given TEAE for a subject, the most severe intensity will be counted. Only actual severity will be used in analysis of AE by severity. Analyses will be performed by treatment groups across all attacks and for each attack. Additionally, TEAEs will be reported at the patient level and at the attack level. Finally, TEAEs will be summarized for selected subsets, such as treated 4 migraine attacks, had recent triptan use, had concurrent use of topiramate, or had concurrent use of propranolol. For the control group, placebo and lasmiditan 50 mg will be evaluated separately.

Other AEs:

Adverse events that are not defined as TEAEs will be considered as other AEs. Frequency counts and percentages will be presented for subjects within each SOC and PT, separated by treatment group.

### 5.5.10.3. Columbia-Suicide Severity Rating Scale

The C-SSRS will be used to assess suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent. At Visit 1, the screening version will be used to assess suicidal

ideation and behavior during the lifetime and in the past 1 month. At Visit 2, Visit 4, and end of study/Visit 6, the Since Last Visit version will be used to assess suicidal ideation and behavior since the last visit.

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent occurring during the study, based on the C-SSRS, will be summarized by treatment group. In particular, for each of the following events, the number and percent of patients with the event will be enumerated by treatment group: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, 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, and self-injurious behavior without suicidal intent.

In addition, the number and percent of patients who experienced at least 1 of various composite measures during the treatment (all visits after randomization) will be presented and compared, separately. Composite measures include suicidal behavior (completed suicide, non-fatal suicidal attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior), suicidal ideation (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, non-specific active suicidal thoughts, and wish to be dead), and suicidal ideation or behavior.

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 and comparative 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 (No 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

Self-injurious behavior without suicidal intent is also a C-SSRS outcome (although not suicide-related) and has a binary response (yes/no).

Composite endpoints based on the above categories are defined below.

- Suicidal ideation: A "yes" answer at any time during treatment to any 1 of the 5 suicidal ideation questions (Categories 1 to 5) on the C-SSRS.
- Suicidal behavior: A "yes" answer at any time during treatment to any 1 of the 5 suicidal behavior questions (Categories 6 to 10) on the C-SSRS.
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any 1 of the 10 suicidal ideation and behavior questions (Categories 1 to 10) on the C-SSRS.

These suicidal ideations, suicidal behaviors, and the composite endpoints of recent history, as well as all prior history collected during the baseline period, will also be summarized by treatment group. The definitions of recent history and all prior history for C-SSRS assessments are: 1) for the recent history: Visit 1 including past 1 month and Visit 2, but with lifetime excluded; 2) for the all prior history: Visit 1 including lifetime and Visit 2 are included.

These suicidal ideations, behaviors, and the composite endpoints during the treatment will also be summarized and compared between treatment groups, by patients with and without any suicidal ideations or behaviors reported in recent history.

Patients who discontinued from the study with no postbaseline C-SSRS value will be considered unevaluable for analyses of suicide-related events. Only evaluable patients will be considered in the analyses. Fisher's exact test will be used for treatment comparisons. For each event, p-values will only be displayed if at least 4 events occurred in at least 1 treatment group.

Listings will present all C-SSRS data for subjects with at least 1 positive response to any C-SSRS question at any time during the study.

### 5.5.10.4. Vital Signs and Weight

Vital signs collected during the study include systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse.

The baseline for SBP, DBP, pulse, and weight is defined as the nonmissing value collected at Visit 1. The postbaseline for SBP, DBP, pulse, and weight is defined as the nonmissing value collected at all visits after randomization (including scheduled Visit 4 and Visit 6/end of study).

*Categorical Analysis:* The number and percentage of patients meeting criteria for treatment-emergent abnormalities in vital signs and weight at any time during study will be summarized by treatment group. Table LAIJ.5.7 displays the criteria used to define treatment-emergent changes in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories; treatment-emergent categorical changes will be analyzed for each of those patient populations.

The criteria generally consist of 2 parts: an absolute threshold and a change from baseline amount. The absolute threshold in the criteria is based on 1) minimum post baseline when the direction is low and, 2) maximum post baseline when the direction is high.

The change from baseline amount in the criteria is 1) decrease from baseline to minimum postbaseline when the direction is low and 2) increase from baseline to maximum post baseline when the direction is high.

**Table LAIJ.5.7. Criteria for Categorical Changes of Interest in Vital Signs and Weight**

| Parameter | Direction | Criteria | Patient Population Defined by Baseline Categories |
|---|---|---|---|
| Systolic BP (mmHg) | Low | ≤90 and decrease ≥20 | All patients; >90; ≤90 |
| | High | ≥140 and increase ≥20 | All patients; <140; ≥140 |
| | PCS High | ≥180 and increase ≥20 | All patients; <180; ≥180 |
| Diastolic BP (mmHg) | Low | ≤50 and decrease ≥10 | All patients; >50; ≤50 |
| | High | ≥90 and increase ≥10 | All patients; <90; ≥90 |
| | PCS High | ≥105 and increase ≥15 | All Patients;<105; ≥105 |
| Pulse (bpm) | Low | <50 and decrease ≥15 | All patients; ≥50; <50 |
| | High | >100 and increase ≥15 | All patients; ≤100; >100 |
| Weight (kg) | Low | (Loss) decrease ≥7% | All patients |
| | High | (Gain) increase ≥7% | All patients |

Abbreviations: BP = blood pressure; bpm = beats per minute; PCS = potentially clinically significant.
Note: "all patients" include all patients in safety population with both non-missing baseline and non-missing postbaseline measure.

In addition, the number and percent of patients with postbaseline blood pressures and pulse in the following categories will be provided by treatment group:

- SBP: ≤90 mmHg, ≥140 mmHg, ≥160 mmHg
- DBP: ≤50 mmHg, ≥90 mmHg, ≥100 mmHg
- Pulse: ≤60 bpm, ≥100 bpm

*Continuous Analysis*

For blood pressure, pulse, and weight, the mean change from baseline to visits (including scheduled Visits 4 and 6) and last-observation-carried-forward (LOCF) endpoint will be conducted on patients who have a baseline and at least 1 postbaseline observation, using an ANCOVA model with treatment group, region, and baseline value as the covariates. In those analyses, values from unscheduled visits will be ignored and only the values collected at the scheduled visit will be used.

### 5.5.10.5. Laboratory Results

For each analyte, the number and percentage of patients with treatment-emergent abnormal, high, or low laboratory results at any time postbaseline will be summarized by treatment group. The definition of baseline is the last non-missing value collected before randomization, and

postbaseline visits include all the visits after randomization. Scheduled visits, unscheduled visits, and repeat measurements will be included as appropriate.

Patients will be defined as having a treatment-emergent low value if they have all normal or high values at baseline, followed by a value below the lower reference limit at any postbaseline visit. Patients with all normal or high values at baseline (no low values) will be included in the analysis of treatment-emergent low laboratory values.

Patients will be defined as having a treatment-emergent high value if they have all normal or low values at baseline, followed by a value above the upper reference limit at any postbaseline visit. Patients with all normal or low values at baseline (no high values) will be included in the analysis of treatment-emergent high laboratory values.

For analytes simply classified as normal or abnormal, patients will be defined as having a treatment-emergent abnormal value if they have all normal values at baseline, followed by an abnormal value at any post-baseline visit. Patients with all normal values at baseline will be included in the analysis of treatment-emergent abnormal laboratory values.

*Abnormal Hepatic Tests*

The number and percentage of patients with the following elevations in hepatic laboratory tests at any time postbaseline will also be summarized for each treatment groups.

- The percentages of patients with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) measurement greater than or equal to 3x , 5x, and 10x the upper limit of normal (ULN) during the treatment period will be summarized for all patients with a postbaseline value.
- The percentages of patients with an alkaline phosphatase (ALP) measurement greater than or equal to 2x the ULN during the treatment period will be summarized for all patients with a postbaseline value.
- The percentages of patients with a total bilirubin (TBL) measurement greater than or equal to 2x ULN during the treatment period will be summarized for all patients with a post-baseline value.

Hy's law is defined as the combination of the following criteria: drug-related elevation of ALT ≥3 x ULN and TBL ≥2 x ULN, in the absence of significant cholestasis (that is, ALP <2 x ULN), and in the absence of other causes of liver injury. Evaluation of a drug-induced serious hepatotoxicity plot will also be provided.

Shift tables describing out of reference range shifts will be provided for clinical laboratory test results from baseline to postbaseline by treatment group.

A listing of hepatic abnormal laboratory results that meet the prespecified categorical thresholds will be provided.

*Continuous Analysis*

For each analyte, the mean change from baseline to LOCF endpoint will be conducted on patients who have a baseline and at least 1 post-baseline observation, using an ANCOVA model with treatment group and baseline value as the covariate. In those analyses, values from unscheduled visits will be ignored and only the value collected at scheduled visit will be used. If repeat laboratory values exist at the same scheduled visit, only the last nonmissing laboratory value at a visit (selected by using the variable with highest laboratory sequence identifier) will be used in the ANCOVA analysis for mean change from last baseline value to LOCF endpoint.

#### 5.5.10.6. Assessment of Driving Incidents

In order to evaluate the impact of lasmiditan on driving, an assessment of driving accidents/violations will be conducted by site personnel at Visit 2, Visit 4, and end of study/Visit 6.

At Visit 2, the baseline version will be used to assess whether patients have been involved in any car accidents or have received any citations/tickets for any moving violations in the past 6 months. At Visit 4 and end of study/Visit 6, the Since Last Visit version will be used to assess car accidents or moving violations since the last visit.

Car accidents and moving violations recorded on the driving assessment at baseline (Visit 2) and during the study (Visit 4 and end of study/Visit 6) will be summarized and compared by treatment group. In particular the number and percent of patients who reported involvement in any car accidents as the driver at the time of that accident, and the number and percent of patients who reported receiving any citations/tickets will be presented. Fisher's exact test will be used for treatment comparisons and p-values will only be displayed if at least 4 patients reported car accidents or moving violations in at least 1 treatment group.

Patients who discontinued from the study with no postbaseline driving assessment will be considered unevaluable for analyses of driving-related accidents and violations. Only evaluable patients will be considered in the analyses.

Assessment of accidents/violations will be listed by patient and treatment group.

### *5.5.11. Subgroup Analyses*

Primary efficacy, consistency endpoints, and pain relief at 2 hours will be performed at minimum for subgroups. The following variables are used to define subgroups.

- age
- sex (female/male)
- weight
- racial origin
- ethnicity (Hispanic versus not)
- triptan experience (triptan-experienced or triptan-naive)
- overall response to triptan (poor/none versus good) (poor/none versus other)

- triptan insufficient responders (TIR versus triptan responders see definition) (TIR versus Other)
- failed 2 or more triptans
- geographical region
- cardiovascular risk factors (4 factors based on ACC/AHA guidance)
- migraine headaches treated more than 4 hours after onset

For triptan experienced (past or present) patients, subgroups are defined based on efficacy results or adherence to treatment. The subgroup of poor or none response to most recent triptan will be analyzed.

The composite triptan insufficient responder are patients who meet any 1 of the following 3 criteria.

1. Triptan inconsistent responders:
   Patients who never achieve pain free at 2 hours or do not achieve pain free in 2 out of 3 attacks with their most recent triptan;
2. Triptan discontinuers due to lack of efficacy, tolerability issues, or contraindications:
   Patients not currently taking a triptan but who discontinued their most recent triptan due to lack of efficacy, tolerability issues, or contraindications as defined below:
   - Lack of pain freedom at 2 hours
   - Lack of pain relief at 2 hours
   - Did not return function or eliminate disability
   - Inconsistent response (pain freedom at 2 hours in <2 out of 3 attacks)
   - Migraine recurrence (within 24 hours)
   - Did not relieve associated symptoms (that is, nausea, vomiting, photophobia or phonophobia)
   - Did not like route of administration
   - Discontinued due to cardiovascular disease or event
   - Discontinued due to cardiovascular risk factors
   - Discontinued due to contraindication or warning
   - Intolerance to medication (tolerability Issues)
3. mTOQ-6 poor/very poor responders:

   Current triptan users with a score of poor or very poor using the mTOQ-6 (score of ≤5 based on results of answers to the following 4 questions (Lipton et al. 2015):
   - After taking your migraine medication, are you pain-free within 2 hours for most attacks?
   - Does 1 dose of your migraine medication usually relieve your headache and keep it away for at least 24 hours?

- Are you comfortable enough with your migraine medication to be able to plan your daily activities?
- After taking your migraine medication, do you feel in control of your migraines enough so that you feel there will be no disruption to your daily activities?

The subgroup of triptan contraindicated is defined as follows: patients who have triptan contraindications (per labels of triptans) based on medical history, in particular, for patients who have the following diseases in medical history:

- Angina pectoris
- Angina unstable
- Myocardial infarction
- Acute myocardial infarction
- Silent myocardial infarction
- Myocardial ischaemia
- Coronary artery disease
- Microvascular coronary artery disease
- Arteriosclerosis coronary artery
- Wolff-Parkinson-White syndrome
- Arrhythmia
- Cerebrovascular accident
- Embolic stroke
- Ischemic stroke
- Transient ischemic attack
- Peripheral vascular disorder
- Raynaud's phenomenon
- Superior mesenteric artery syndrome
- Labile hypertension

Descriptive statistics will be provided for each treatment and stratum of a subgroup as outlined, regardless of sample size.

For subgroup analysis, 2 types of comparisons will be made to test similarity of treatment effect. First the subgroup will be compared with the rest of patients in the total population. Second, for subgroups which are part of triptan experienced subgroup, the comparison will be made for the subgroup versus patients having a complementary response (for example, poor triptan responder versus good triptan responder).

Subgroup analyses for categorical outcomes will be performed via logistic regression for binary response variables. The model will include the categorical outcome as the dependent variable and baseline value, country or region, treatment, subgroup, and treatment-by-subgroup interaction as explanatory variables. The treatment-by-subgroup interaction will be tested at the 0.1 significance level. The p-value from the logistic regression model will be reported for the interaction test and the subgroup test, unless the model did not converge. Response counts and percentages will be summarized by treatment for each subgroup category. The odds ratio and 95% confidence interval (CI) versus placebo will be reported for each subgroup category.

Subgroup analyses for continuous outcomes will be performed via ANCOVA. The model will include the continuous outcome as the dependent variable and baseline value, region, treatment, subgroup, and treatment-by-subgroup interaction as explanatory variables. The treatment-by-subgroup interaction will be tested at the 0.1 significance level. The p-value from the ANCOVA model will be reported for the interaction test and the subgroup test. Response variable will be summarized by treatment for each subgroup category.

For gated subgroup analysis (for example, for triptan insufficient responder subgroups), a separate analysis will be performed for such subgroup, and p-values will be used in gatekeeping.

In the case that any level of a subgroup comprises <10% of the overall sample size, only descriptive summary statistics will be provided for treatment groups, and no treatment group comparisons will be performed within these subgroup levels.

An additional subgroup analysis will be done for first attack pain freedom using the same criteria as before, but requiring patients to have insufficient response on their last 2 triptans (not just their last triptan).

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

### *5.5.12. Additional Analysis for Triptan Insufficient Responder Subpopulation*

To evaluate the efficacy of lasmiditan 200 mg and 100 mg in triptan insufficient responders subpopulation, the following analyses will be conducted:

The proportions of patients in the subpopulation of triptan insufficient responders that achieve primary and secondary objectives and selected exploratory objectives in each group. Analyses will be conducted for the first attack and all attacks, as appropriate, to compare lasmiditan versus placebo or control. As for the overall populations (ITT, mITT, ITT consistency, and mITT consistency), the same model will used for this subpopulation and inferential statistics (that is, odds ratios and 95% confidence interval, p-values of comparisons of lasmiditan doses versus placebo or control, etc) will be displayed.

Furthermore, baseline characteristics are summarized to check balance (for example, age, sex) among treatment groups.

### *5.5.13. Sensitivity Analysis*

A sensitivity analysis will be performed for first attack. The binary response variable is the indicator of pain-free or pain-relief at postdose time points (0.5, 1, and 2 hours after dosing).

The response variables will be analyzed using a categorical, pseudo-likelihood-based repeated measures analysis. This analysis will be implemented using the GLIMMIX procedure in SAS to compare treatments for 1 hour and 2 hours after dosing with covariates adjustment.

The analysis includes the fixed categorical effects of treatment (placebo, lasmiditan 100 mg, and lasmiditan 200 mg), time point (0.5, 1, and 2 hours after dosing), and treatment-by-time point interaction as well as the fixed categorical covariates of geographic region.

An unstructured covariance structure will be used to model the within-patient errors (denoted by TYPE=CHOL in the RANDOM statement). The Newton-Raphson method with ridging will be used for nonlinear optimization (denoted by including NLOPTIONS TECH=NRRIDG). The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. If the model does not converge, the Fisher's exact test scoring algorithm will be utilized by the SCORING option in SAS.

If the model still fails to converge, the model will be fit using covariance matrices in the following order specified by a decreasing number of covariance parameters until convergence is met:

1. Heterogeneous Toeplitz
2. Heterogeneous first-order autoregressive
4. Toeplitz
5. First-order autoregressive

If necessary, both fitting algorithms will be used in the pre-specified order before proceeding to the next covariance structure in the sequence.

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.

For models where the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters.

The sandwich estimator is utilized by the EMPIRICAL option in SAS. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between subject and within-subject portions by the DDFM=BETWITHIN option in SAS.

A sample SAS code for this analysis using SAS procedure GLIMMIX is the following:

```
PROC GLIMMIX DATA=data
CLASS REGION TRT TIME USUBJID;
MODEL AVALC(EVENT ='Y') =REGION TRT TIME TRT*TIME/DDFM=KR
SOLUTION LINK=LOGIT DIST=BINARY;
RANDOM RESIDUAL / subject=USUBJID TYPE=CHOL Residual;
RUN;
```

The lasmiditan 100 mg and 200 mg will be compared with placebo at the 1 hour and 2 hour post-dose time points.

Some patients had their MIDAS data collected over the telephone because of COVID-19 considerations. Sensitivity analyses will exclude these patients.

During the conduct of the study, an eDiary issue emerged requiring a software update. Analyses will be conducted to evaluate whether there was any impact of this software update.

Additionally, summary analyses investigating the possible impact of missing data / differently collected data during COVID-19 will be performed. Such summaries include summarization of pain freedom data recorded after 01 February 2020 to those recorded prior to 01 February 2020 as well as the comparison of AE rates for events occurring on or after 01 February 2020 to those occurring prior to 01 February 2020.

## 5.6. Main Database Lock and Additional Sensitivity Analysis Database Lock Based on COVID-19

Because of COVID-19 considerations, some patients were unable to attend sites for their final visits in person. Because primary and gated secondary endpoint data are based upon eDiary collection and did not require an onsite visit, a final efficacy analysis will be conducted based on the main database lock. Subsequently, some patients may be able to return to the sites and undergo final safety assessments including vital signs, laboratory collection, etc. After this data is collected, an additional database lock will be conducted and sensitivity analyses will be performed.

## 5.7. Unblinding Plan

A designated study team member in collaboration with the project statistician will be responsible for keeping a running log of individuals given access to any unblinded study data. This log will include the person's name, title, date of unblinding, level of unblinding (that is, group or patient), and purpose of unblinding. The functions listed in Table LAIJ.5.8 have access to the treatment information; however, they are not allowed to join meetings that may affect the other members' blinded status, such as trial-level safety review and data review meetings.

**Table LAIJ.5.8. Unblinded Members through Study LAIJ**

| Role | Reason | Data Source for Unblinding |
|---|---|---|
| Product Delivery Personnel | To provide and manage clinical trial materials | e-CTS |
| Unblind Case Manager | To report SAE with unblinded information to EU authority | e-CTS |
| Clinical Laboratory Operations | To manage and track sample shipping | CLRM |

Abbreviations: CLRM = Clinical Laboratory Results Modernization; e-CTS = Enhanced Clinical Trials System; IWRS = interactive web-response system; SAE = serious adverse event.

Version 2 of the blinding and unblinding plan is attached in Appendix 1.

## 5.8. Clinical Trial Registry Analyses

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

Analyses provided for the CTR requirements include the following:

A summary of AEs will be provided as a dataset that will be converted to an XML file. Both SAEs and 'Other' AEs are summarized by treatment group and MedDRA PT.

- An AE is considered 'Serious' whether or not it is a TEAE (definitions of AE and TEAE are provided in Section 5.5.10).
- An AE is considered in the 'Other' category if it is both a TEAE and is not serious. For each SAE and 'Other' AE, for each term and treatment group, the following are provided:
    1. the number of participants at risk of an event
    2. the number of participants who experienced each event term
    3. the number of events experienced.
- AE reporting is consistent with other document disclosures (for example, CSR, manuscripts)

# 6. Important Protocol Deviations

Note: deviation is derived for each treated attack when applicable. A patient having any deviation on the first attack indicated by a superscript [a] is excluded from per protocol analysis for first attack; a patient having deviations indicated by a superscript [b] with any attack will be excluded from the per protocol analysis for consistency assessment; and deviation with superscript [d] will be excluded from efficacy per protocol analysis for OLE.

## 6.1. Inclusion/Exclusion Criteria

All inclusion/exclusion criteria deviations are important protocol deviations. Functional areas immediately notify the study manager of all inclusion/exclusion criteria deviations that they identify.

| I/E Number or Term | Category | Sub-category | Trial-specific Term | Excluded Per Protocol Set (Y/N/NA) |
|---|---|---|---|---|
| [1] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age at time of screening (Visit 1) with migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 or 1.2.1 (ICHD-3; see Appendix 5) | Eligibility | Inclusion/ Exclusion | Not of an appropriate age to provide informed consent | Y |
| [1] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age at time of screening (Visit 1) with migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 or 1.2.1 (ICHD-3; see Appendix 5) | Eligibility | Inclusion/ Exclusion | Less than 18 years of age at V1 | Y |
| [1] are of an acceptable age to provide informed consent according to the local regulations and are at least 18 years of age at time of screening (Visit 1) with | Eligibility | Inclusion/ Exclusion | Pt does not meet IHS diagnostic criteria 1.1 or 1.2.1 | Y |

| I/E Number or Term | Category | Sub-category | Trial-specific Term | Excluded Per Protocol Set (Y/N/NA) |
|---|---|---|---|---|
| migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 or 1.2.1 (ICHD-3; see Appendix 5) | | | | |
| [2] history of disabling migraine for at least 1 year | Eligibility | Inclusion/ Exclusion | Pt has not had disabling migraine for at least 1 year | Y |
| [3] migraine onset before the age of 50 years | Eligibility | Inclusion/ Exclusion | Pt did not have migraine onset before age 50 | Y |
| [4] history of 3 to 8 migraine attacks per month (<15 headache days per month) during the past 3 months | Eligibility | Inclusion/ Exclusion | Pt has <3 or >8 attacks/mo, >15 headache days/mo, in past 3 mo | Y |
| [5] MIDAS score ≥11 | Eligibility | Inclusion/ Exclusion | Pt has MIDAS score less than 11 | Y |
| [10] known hypersensitivity to lasmiditan, or to any excipient of lasmiditan oral tablets | Eligibility | Inclusion/ Exclusion | Known hypersensitivity to lasmiditan | Y |
| [11] history or evidence of hemorrhagic stroke, epilepsy, or any other condition placing the patient at increased risk of seizures | Eligibility | Inclusion/ Exclusion | Hx of stroke, epilepsy, or other risk of seizures | Y |
| [12] history of recurrent dizziness and/or vertigo including benign paroxysmal positional vertigo, Meniere's disease, vestibular migraine, and other vestibular disorders | Eligibility | Inclusion/ Exclusion | Hx of recurrent dizziness and or vertigo | Y |
| [13] history of diabetes mellitus with complications (diabetic retinopathy, nephropathy, or | Eligibility | Inclusion/ Exclusion | Hx of diabetes with complications | Y |

| I/E Number or Term | Category | Sub-category | Trial-specific Term | Excluded Per Protocol Set (Y/N/NA) |
|---|---|---|---|---|
| neuropathy) | | | | |
| [14] history of orthostatic hypotension with syncope | Eligibility | Inclusion/ Exclusion | Hx of orthostatic hypotension with syncope | Y |
| [15] significant renal or hepatic impairment in the opinion of the investigator or if they meet hepatic monitoring criteria (see Section 9.4.5.1) | Eligibility | Inclusion/ Exclusion | Significant renal or hepatic impairment | Y |
| [16] patients who, in the investigator's judgment, are actively suicidal and therefore deemed to be at significant risk for suicide, or those who have answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C–SSRS, or answer "yes" to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act or behavior) on the "Suicidal Behavior" portion of the C–SSRS; and the ideation or behavior occurred within the past month of Visit 1 or 2 | Eligibility | Inclusion/ Exclusion | Pt is deemed significant suicide risk | Y |
| [18] history, within past 12 months, of chronic migraine or other forms of primary or | Eligibility | Inclusion/ Exclusion | Hx of chronic migraine or other chronic headache disorder | Y |

| I/E Number or Term | Category | Sub-category | Trial-specific Term | Excluded Per Protocol Set (Y/N/NA) |
|---|---|---|---|---|
| secondary chronic headache disorder (for example, hemicranias continua, medication overuse headache where headache frequency is ≥15 headache days per month [Appendix 5]) | | | | |
| [19] use of more than 3 doses per month of either opioids or barbiturates | Eligibility | Inclusion/ Exclusion | Use of >3 doses per month of opioids or barbiturates | Y |
| [20] initiation of or a change in concomitant medication to reduce the frequency of migraine episodes within 3 months prior to Screening/Visit 1 | Eligibility | Inclusion/ Exclusion | Initiation or change in migraine prophylaxis 3 mo prior to V1 | Y |
| [21] female patients who are pregnant or breast-feeding | Eligibility | Inclusion/ Exclusion | Female patients who are pregnant or breastfeeding | Y |
| [22] women of child-bearing potential who test positive for pregnancy based on a serum pregnancy test collected at Visit 1 | Eligibility | Inclusion/ Exclusion | WOCBP with positive serum pregnancy test at V1 | Y |
| [23] history of drug or alcohol abuse/dependence within 1 year prior to Visit 1 (excessive or compulsive use as judged by the investigator), or currently using drugs of potential abuse or any prescribed or over-the-counter medication in a manner that the investigator considers indicative of abuse/dependence | Eligibility | Inclusion/ Exclusion | Hx of drug/alcohol abuse or dependence within 1 yr prior to V1 | Y |

| I/E Number or Term | Category | Sub-category | Trial-specific Term | Excluded Per Protocol Set (Y/N/NA) |
|---|---|---|---|---|
| [24] have a positive urine drug screen for any substances of abuse at Visit 1 Note: A retest is allowed if the urine drug screen is positive for any prescribed substance or if, in the judgment of the investigator, there is a medically acceptable explanation for the positive result. The results of the retest must be negative at or prior to Visit 2 | Eligibility | Inclusion/ Exclusion | Pt has positive urine drug screen at V1 | Y |
| [25] have an acute, serious or unstable medical condition, or a history or presence of any other medical illness including but not limited to any autoimmune disease, CV, hepatic, respiratory, hematological, endocrine, psychiatric, or neurological disease, or any clinically significant laboratory abnormality, that, in the judgment of the investigator, indicates a medical problem that would preclude study participation | Eligibility | Inclusion/ Exclusion | Pt has acute, serious or unstable medical condition | Y |
| [26] known hypersensitivity to multiple drugs | Eligibility | Inclusion/ Exclusion | Known hypersensitivity to multiple drugs | Y |
| [32] treated at least 3 migraine attacks in the main study with study drug | Eligibility | Inclusion/ Exclusion | OLE only: Did not treat at least 3 migraine attacks in main | Y |
| [33] were not discontinued early from the main study | Eligibility | Inclusion/ Exclusion | OLE only: Pt DC'd early from main study | Y |

| I/E Number or Term | Category | Sub-category | Trial-specific Term | Excluded Per Protocol Set (Y/N/NA) |
|---|---|---|---|---|
| [34] do not meet discontinuation criteria described in Section 8 of the main protocol | Eligibility | Inclusion/ Exclusion | OLE only: Pt meets DC criteria of main study | Y |
| [35] were sufficiently compliant with the main study protocol in the opinion of the investigator to proceed into this OLE | Eligibility | Inclusion/ Exclusion | OLE only: Pt was non-compliant with main study | Y |
| [38] if, in the opinion of the investigator, does not respond to treatment with conventional analgesics, such as acetaminophen or nonsteroidal anti-inflammatory medications | Eligibility | Inclusion/ Exclusion | DE only: Pt does not respond to tx with conventional analgesics | Y |
| [39] is currently committed to an institution by administrative or judicial order | Eligibility | Inclusion/ Exclusion | DE only: Pt currently committed to an institution | Y |
| [36] routinely uses triptans, ergot preparations, opioids, or barbiturates to treat their migraine attacks in the opinion of the investigator | Eligibility | Inclusion/ Exclusion | CZ only: Pt routinely uses excluded con meds to treat migraine | Y |
| [37] has had an MRI or other neuroimaging result that shows a clinically relevant neurological condition (such as significant neoplasm or intracranial infection) that makes the patient unsuitable for participating in the study in the opinion of the investigator | Eligibility | Inclusion/ Exclusion | IN only: Neuro imaging shows clinically relevant neuro condition | Y |
| I/E #6 through 9 and I/E# 27 through 31 | Eligibility | Inclusion/ Exclusion | Other: Inadvertent Enrollment | Y |

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; CV = cardiovascular; CZ =Czech Republic ;DC = discontinued; DE =Germany ; Hx = history; ICHD = International Classification of Headache Disorders 3rd edition; IHS = International Headache Society; IN =India ; MIDAS = Migraine Disability Assessment Test; mo = month; MRI = magnetic resonance imaging; N = no; NA = not applicable; OLE = open-label extension; Pt = patient; tx = treatment; V = visit; WOCBP = women of child-bearing potential; Y = yes; yr = year.

## 6.2. Other Important Protocol Deviations

Functional areas immediately notify the study manager of IPDs that they identify per the table below.

| Category | Sub-category | Trial-specific Term | Programmable by Stats (Y/N) | Excluded Per Protocol Set (Y/N/NA) | Immediate Notification (Y/N) |
|---|---|---|---|---|---|
| Informed Consent | Informed Consent Not Obtained | Procedure done prior to or without consent | Y | Y | Y |
| Informed Consent | Informed Consent Not Obtained | No reconsent for safety update | N | Y | Y |
| Informed Consent | Improper Consent | Pt consented to wrong version of ICF | N | N | Y |
| Safety | SAEs | Not reported in 24 hours | N | N | Y |
| Study Procedures | Visit Schedule Criteria | Missing eDiary data at time point 0 hr | N | Y[a,b] | Y |
| Study Procedures | Visit Schedule Criteria | Missing EQ-5D eDiary data at time point 0 hr | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing eDiary data at time point 2 hr | Y | Y[a,b] | Y |
| Study Procedures | Visit Schedule Criteria | Missing eDiary data at time point 24 hr during 1st attack | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing eDiary data at time point 48 hr during 1st attack | Y | N | N |

| Category | Sub-category | Trial-specific Term | Programmable by Stats (Y/N) | Excluded Per Protocol Set (Y/N/NA) | Immediate Notification (Y/N) |
|---|---|---|---|---|---|
| Study Procedures | Visit Schedule Criteria | Missing PGIC eDiary data at time point 2 hr during 1st attack | Y | N | Y |
| Study Procedures | Visit Schedule Criteria | Missing MQoLQ data at time point 24 hr during 1st attack | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing MIDAS data at baseline | Y | Y | Y |
| Study Procedures | Visit Schedule Criteria | Missing MIDAS data at V6 or EOS | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing mTOQ6 at V2 or EOS | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing Treatment Satisfaction at EOS | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing PGIS at baseline or EOS | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing PGIC-MHC at EOS | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing MSQ at V6 or EOS | Y | N | N |
| Study Procedures | Visit Schedule Criteria | Missing 1 or + OLE Diary (sev, dose, dose time, reason not take IP) | Y | N | N |
| Study Procedures | Violation of Discontinuation Criteria | Study Treatment | N | N | Y |
| Study Procedures | Violation of Discontinuation Criteria | Hepatic Impairment | N | N | Y |

| Category | Sub-category | Trial-specific Term | Programmable by Stats (Y/N) | Excluded Per Protocol Set (Y/N/NA) | Immediate Notification (Y/N) |
|---|---|---|---|---|---|
| Study Procedures | Violation of Discontinuation Criteria | Liver Test Abnormality | N | N | Y |
| Study Procedures | Violation of Discontinuation Criteria | Suicidality | Y | N | Y |
| Study Procedures | Violation of Discontinuation Criteria | Pt becomes Pregnant or is breastfeeding | N | N | Y |
| Study Procedures | Excluded Conmeds | Pt took med other than IP as 1st treatment prior to IP | Y | Y[a,b] | N |
| Study Procedures | Excluded Conmeds | Pt took rescue/recurrence med within 2 hrs of IP | Y | Y[a,b] | N |
| Study Procedures | Excluded Conmeds | Pt took excluded med within 24 hrs after IP | N | Y[a,b] | N |
| Study Procedures | Excluded Conmeds | Pt took IP within 24 hrs after excluded med | N | Y[a,b] | N |
| Study Procedures | Excluded Conmeds | Pt took prophylaxis tx with an end date after V1 | Y | Y[a,b] | Y |
| Study Procedures | Excluded Conmeds | Pt initiated new prophylactic tx after V1 | Y | Y[a,b] | Y |
| Study Procedures | Lab/Imaging Criteria | Hepatic monitoring kit not collected | N | N | Y |
| Study Procedures | Lab/Imaging Criteria | Missing lab at baseline or not having at least 1 postbaseline | Y | N | N |
| Study Procedures | Visit Schedule | Missing vitals at | Y | N | N |

| Category | Sub-category | Trial-specific Term | Programmable by Stats (Y/N) | Excluded Per Protocol Set (Y/N/NA) | Immediate Notification (Y/N) |
|---|---|---|---|---|---|
| | Criteria | baseline or not having at least 1 postbaseline | | | |
| Study Procedures | Visit Schedule Criteria | Missing ECG collection | Y | N | N |
| Study Procedures | Equipment | eDiary not dispensed by site at V2 | N | N | Y |
| Investigational Product | Other | Improper destruction/return of IP to Lilly | N | N | Y |
| Administration/ Oversight | Improper conduct of assessment | C-SSRS scale administered by unqualified rater | N | N | Y |
| Administration/ Oversight | Improper conduct of assessment | IP completed by site personnel instead of patient | N | N/A | N |
| Administration/ Oversight | Improper conduct of assessment | Incorrect version of MIDAS recall period completed at visit | N | N | N |
| Investigational Product | Dosing Error | Overdose of IP | N | Y[a,b] | Y |
| Investigational Product | Dosing Error | 2nd dose taken within 48 hours with first attack (DB period only) | Y | Y[a] | Y |
| Investigational Product | Dosing Error | 2nd dose taken within 48 hours with attack 2, 3, or 4 (DB period only) | Y | Y[b] | Y |
| Investigational Product | Dosing Error | 2nd dose taken within 24 hours (OLE period only) | Y | Y[d] | N |

Abbreviations: C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double blind; ECG = electrocardiogram; EOS = end of study; EQ-5D = EuroQol 5-dimension; hr = hour; ICF = informed consent form; IP = investigational product; med = medication; MHC =Migraine Headache Condition; MIDAS = Migraine Disability Assessment Test; MQoLQ = Migraine Quality of Life Questionnaire; MSQ =Migraine specific Quality of Life Questionnaire ; mTOQ6 = Migraine Treatment Optimization Questionnaire 6 scores; N = no; NA = not applicable; OLE = open-label extension; PGIC = Patient Global Impression of Change; Pt = patient; SAE = serious adverse event; sev = severity; tx = treatment; V = visit; WOCBP = women of child-bearing potential; Y = yes.

# 7. References

Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;28(4):586-604.

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

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

Lipton RB, Fanning KM, Serrano D, Reed ML, Cady R, Buse DC. Ineffective acute treatment of episodic migraine is associated with new-onset chronic migraine. *Neurology* 2015;84(7):688-695.

# 8. Appendices

# Appendix 1. Blinding and Unblinding Plan Version 2.0

# 1. Blinding and Unblinding Plan for Protocol H8H-MC-LAIJ Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Lasmiditan Over Four Migraine Attacks



Lasmiditan (LY573144) Migraine Attacks

Eli Lilly and Company
Indianapolis, Indiana USA 46285
Protocol H8H-MC-LAIJ

# 2. Table of Contents

## List of Tables

## 3. Revision History

Blinding and Unblinding Plan Version 1 was approved prior to primary database lock. Previous information around blinding and unblinding were captured in within the LAIJ version 1 statisticial analysis plan.

# 4. Objective of Blinding and Unblinding Plan

The objective of this Blinding and Unblinding Plan for Study LAIJ is to serve as a source for operational details, roles, and responsibilities around delivering data, either datasets, such as raw data, standard data tabulation model (SDTM), and analysis data model (ADaM) datasets, or tables, figures, and listings (TFLs) in either a blinded or unblinded fashion per the objectives of the protocol and the protocol addendum.

This Blinding and Unblinding Plan details the procedures in place to minimize bias while preparing for or conducting any summary or analysis of Study LAIJ for data reviews, including the development safety update report (DSUR), trial-level safety reviews (TLSRs), or other regulatory purposes, and for interim analysis and primary analysis, which will be used for the interim safety analysis and clinical study report (CSR), respectively.

## 4.1. Global Study Per Protocol

All patients enrolled as described in the main protocol of Study LAIJ will be referred to as the "global cohort."

All patients enrolled as described in the open label extension of Study LAIJ will be referred to as the "LAIJ OLE cohort."

As originally described in the LAIJ protocol and statistical analysis plan (SAP), the primary database lock and unblinding will occur global cohort completion of the Study LAIJ double blind period ; whereas no further unblinding for the global cohort is needed. An additional database lock will occur for the global cohort at a later date, and will include additional data from patients that had their visit schedule disrupted due to COVID-19. As efficacy data are primarily captured through continuous uploads of electronic diaries, very little additional efficacy data are expected after the primary database lock. A separate team of medical, statistical and project management personnel will be kept blinded to individual patient treatment allocation and will be responsible for further database cleaning / query resolution activites after the primary database lock upt until the completion of this additional lock.Maximized Extended Enrollment (ME2) Addendum

The ME2 addendum enables patient enrollment in Study LAIJ to continue in specific geographies (namely China, Russia, and India) to fullfil localregistration requirements after globle cohort enrollment is completed. Patients enrolled in extended portion will be referred to as the maximized extended enrollment (ME2) cohort.

Since all ME2 patients will be randomized after the last patient randomized for the global protocol (Feburary 12, 2020), the randomization datewill be used to differentiate ME2 cohort and OLE cohort (refer to section 4.2) from the global cohort.

Patients within the ME2 cohort for each country will remain blinded until the corresponding country's ME2 addendum enrollment is completed and the corresponding ME2 country cohort database is locked.

## 4.2. Open-Label Extension (OLE) Addendum

The OLE addendum, where approved by local country ERB and Regulatory Authorities, enables certain patients previously enrolled in the LAIJ main study to receive open-label lasmiditan for up to 1 year. Patients enrolled in this Addendum will be referred as Open-Label Extension (OLE) cohort. The OLE addendum was not offered to patients in China, Russia, or India. Therefore, patients from the ME2 cohort will not be in the OLE cohort.

Since this cohort is an open-label flexible dosing cohort, blinding/unbliding is not applicable.

# 5. Creating the Blind: General Blinding Requirements Specific to Study LAIJ

## 5.1. Global Study Per Protocol

For Study LAIJ, the following data must be blinded to patients, sites, and study team members before the primary database is locked for the global cohort:

- Treatment assignment (data TRTASGN) and dose dispersion (data TRTDSPN) from the interactive web-response system (IWRS)

Treatment assignments are blinded in the IWRS and will be unblinded and transferred to the CLUWE system by the Global_DSS_CDTS (global_dss_cdts@lists.lilly.com) ) after the primary database lock for the global cohort. Only personnel from the functions listed below are unblinded to the treatment assignment prior to this primary database lock:

- IWRS support team
- Global_DSS_CDTS associates
- Demand forecasters and clinical supply coordinators from the Clinical Trial Material Supply Chain Planning Team.

## 5.2. ME2 Addendum

For the ME2 cohort(s), the following data must be blinded to patients, sites, and study team members throughout the entire study until the ME2 addendum (including Post-Treatment Follow-Up) is completed within the corresponding country and the database for the ME2 cohort is locked:

- Treatment assignment (data TRTASGN) and dose dispersion (data TRTDSPN) from the interactive web-response system (IWRS)

Only personnel from the functions listed below are unblinded to the treatment assignment and/or those laboratory analytes results before the database lock of ME2 study addendum:

- IWRS support team
- Global_DSS_CDTS associates
- Demand forecasters and clinical supply coordinators from Clinical Trial Material Supply Chain Planning Team
- A designated team of statistical analysts separate from those supporting global cohort primary database lock efforts and analyses: this team is comprised of 2 statistical analysts (programmers) firewalled from the study team. This team will be unblinded to these data after the global cohort primary database lock, and will provide the study team the unblinded global cohort data and blinded ME2 data after the global cohort primary database lock and before the database lock of ME2 study addendum.

## 5.3. Global Study Per Protocol and ME2 Addendum

For the entire study including ME2 addendum, if unintentional unblinding occurs, the following will happen:

- When a subject's treatment group is unexpectedly unblinded during the Blinded Treatment Dosing Period and the unblinding occurs at a site, the monitor or site manager will be notified.
- When a subject's treatment group is unexpectedly unblinded during the Blinded Treatment Dosing Period and the unblinding occurs at a location other than the site, the person who identifies the unblinding will notify his or her immediate supervisor or Medical Quality (MQ) representative in accordance with the requirements described in the Deviation Management procedure: Safety and Efficacy Quality System – Quality (SEQSQ 104-001).

The procedure for emergency unblinding is described in Section 6.3 of the protocol.

If they occur, unintentional unblinding and emergency unblinding will be documented accordingly in the primary CSR for the global cohort, or in the report for the overall Chinese patient population.

After the primary database lock, study team members will be unblinded to the data of the global cohort, but remain blinded to the data of the ME2 cohort. After the ME2 addendum database lock, study team members will be unblinded to the data of the ME2 cohort.

Unblinding sites and patients to treatment assignment for patients enrolled in Global cohort, except those countries participating in the ME2 addendum (China, Russia, India), occur after the primary CSR is completed and distributed. Sites that have patients enrolled in the ME2 addendum will not be unblinded to treatment assignment for patients enrolled in global cohort or ME2 cohort until after the report for the overall ME2 patient population is completed and distributed.

# 6. Details of Maintaining the Blind

The details of maintaining the blind of data for each deliverable type during the global study and ME2 addendum are presented in Table 1.

**Table 1. Details of Maintaining the Blind of Data**

| Data to Be Blinded (Source) | Blinded Data Format | Deliverable Type | How Data Will Be Blinded |
|---|---|---|---|
| Treatment assignment (IWRS) | Global cohort and ME2 cohort: raw data and all subsequent deliverables based on the raw data (SDTM, ADaM, TFLs, or customized datasets/reports) | Test transfers before primary lock;<br>DSURs or other regulatory transfers before primary lock;<br>TLSRs before primary lock | Scrambled data |
| | ME2 cohort:<br>raw data and all subsequent deliverables based on the raw data (SDTM, ADaM, TFLs, or customized datasets/reports) | Global cohort primary database lock;<br>All transfers require unblinded Global cohort data (including DSURs and other regulatory transfers) after global cohort primary lock and before ME2 addendum lock | Scrambled data for ME2 cohort by a designated blinded/unblinded team of statistical analysts |

Abbreviations: ADaM = analysis data model; DSUR = development safety update report; GLS = Generic Lab System; IWRS = interactive web-response system; ME2 = maximized extended enrollment; SDTM = standard data tabulation model; TFLs = tables, figures, and listings; TLSRs = trial-level safety reviews.

After the primary database lock, only the data from the global cohort will be unblinded. The data from the ME2 cohort will remain blinded to sites, patients and study team in the database by utilizing a designated blinded/unblinded team of statistical analysts.

After the ME2 addendum database lock for a given country, the data from the corresponding ME2 cohort will be unblinded. The entire database will be transferred to generate all patients' SDTM/ADaM datasets and TFLs for the overall patient population.

Table 2 provides the details of blinded and unblinded data transfers, including the functions to deliver the data and the locations of the data for the deliverables.

**Table 2. Blinded and Unblinded Data Transfers and Locations**

| Blinding Status | Data Format | Function to Deliver Data[a] | Deliverable Type | CLUWE Location | Additional Sources |
|---|---|---|---|---|---|
| Blinded for both global cohort and ME2 cohort | Raw data: both global cohort and ME2 cohort (All) | Lilly DSS | Test transfers before Global cohort primary lock | \lillyce\qa\ly573144\h8h_mc_laij\prelock\data\raw\shared | Sources: CLRM IWRS, DMV/ALSC eCOA |
| | | | DSURs before Global cohort primary lock | \\lillyce\prd\ly573144\h8h_mc_laij\regulatory_sep***yyyy***\data\raw\shared | |
| | | | TLSRs before Global cohort primary lock | \lillyce\prd\ly573144\h8h_mc_laij\safety_review***n***\data\raw\shared | |
| | | | Other regulatory transfers before Global cohort primary lock | \lillyce\prd\ly573144\h8h_mc_laij\regulatory_***mmmyyyy***\data\raw\shared | |
| | SDTM: All | Lilly Statistics | Test transfers before Global cohort primary lock | \lillyce\qa\ly573144\h8h_mc_laij\intrm1\data\observed\shared | |
| | | | TLSRs before Global cohort primary lock | \lillyce\prd\ly573144\h8h_mc_laij \safety_review***n***\data\observed\shared | |
| | | | Other regulatory transfers before Global cohort primary lock that require SDTM | \lillyce\prd\ly573144\h8h_mc_laij \regulatory_***mmmyyyy***\data\observed\shared | |
| | ADaM: global cohort only | Lilly Statistics | Test transfers before Global cohort primary lock | \lillyce\qa\ly573144\h8h_mc_laij \intrm1\data\analysis\shared | |
| | TFLs: global cohort only | Lilly Statistics | Test transfers before Global cohort primary lock | \lillyce\qa\ly573144\h8h_mc_laij \intrm1\ output\shared | |
| | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Unblinded for global cohort and blinded for ME2 cohort | Raw data: All | inVentiv Global_DSS_CDTS and designated blinded/unblinded team of statistical analysts | Global cohort primary locks (intrm1 intrm2)<br><br>Global cohort final lock (final) | IWRS data stored in \lillyce\prd\ly573144\h8h_mc_laij \misc1\data\raw\restricted<br><br>After SAC stored in<br><br>\lillyce\prd\ly573144\h8h_mc_laij \intrm1\data\raw\restricted<br><br>All other data in<br><br>\lillyce\prd\ly573144\h8h_mc_laij \intrm1\data\raw\restricted<br><br>Use misc2 for intrmand and use misc3 for final lock in the above plan for intrm1. | Sources: IWRS |
| | | | Test transfers after Global cohort primary lock and before ME2 addendum lock | \lillyce\qa\ly573144\h8h_mc_laij \prelock\data\raw\shared | Sources: IWRS, |
| | | | TLSRs after Global cohort primary lock and before ME2 addendum lock | \lillyce\prd\ly573144\h8h_mc_laij\safety_review***n***\data\raw\shared | |
| | | | DSURs after Global cohort primary lock and before ME2 addendum lock | \lillyce\prd\ly573144\h8h_mc_laij\regulatory_sep***yyyy***\data\raw\shared | |
| | | | Other regulatory transfers after Global cohort primary lock and before ME2 addendum lock | \lillyce\prd\ly573144\h8h_mc_laij\regulatory_***mmmyyyy***\data\raw\shared | |

| | | | | | |
|---|---|---|---|---|---|
| | SDTM: All | Lilly Statistics | Global cohort primary locks | \lillyce\prd\ ly573144\h8h_mc_laij \intrm1\data\observed\restricted\<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \intrm2data\observed\restricted\ | |
| | | | Global cohort final lock | If global cohort final lock occurs before ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\data\observed\restricted\<br><br>If global cohort final lock occurs after ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\data\observed\shared\ | |
| | | | Test transfer after Global cohort primary lock and before ME2 addendum lock | \lillyce\qa\ly573144\h8h_mc_laij\prelock\data\observed\shared | |
| | | | Other regulatory transfers after Global cohort primary lock and before ME2 addendum lock that require SDTM | \lillyce\prd\ly573144\h8h_mc_laij\regulatory_***mmmyyyy***\data\observed\shared | |
| | ADaM: global cohort only | Lilly Statistics | Global cohort primary interim locks | \lillyce\prd\ ly573144\h8h_mc_laij \intrm1\data\analysis\restricted<br><br>lillyce\prd\ ly573144\h8h_mc_laij \intrm2\data\analysis\restricted | |

| | | | | | |
|---|---|---|---|---|---|
| | | | Global cohort final lock | If global cohort final lock occurs before ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\data\observed\restricted\<br><br>If global cohort final lock occurs after ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\data\observed\shared\ | |
| | | | Test transfers after global cohort interim locks and before ME2 addendum lock that require ADaM | \lillyce\qa\ ly573144\h8h_mc_laij \final\data\analysis\shared | |
| | | | Other regulatory transfers after Global cohort primary lock and before ME2 addendum lock that require ADaM | \lillyce\prd\ly573144\h8h_mc_laij\regulatory_***mmmyyyy***\data\analysis\shared | |
| | ADaM: All | Lilly Statistics | Test transfers after global cohort final lock and before ME2 addendum lock | \lillyce\qa\ ly573144\h8h_mc_laij\prelock\data\analysis\shared | |
| | TFLs: global cohort only | Lilly Statistics | Global cohort final lock | If global cohort final lock occurs before ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\output\restricted<br><br>If global cohort final lock occurs after ME2 addendum lock<br><br>lillyce\prd\ ly573144\h8h_mc_laij \final\output\shared | |

| | | | | | |
|---|---|---|---|---|---|
| | | | Test transfers after interim lock and before global cohort final lock | \lillyce\qa\ ly573144\h8h_mc_laij \final\output\shared | |
| | | | Global cohort final lock | If global cohort final lock occurs before ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\data\observed\restricted\<br><br>If global cohort final lock occurs after ME2 addendum lock<br><br>\lillyce\prd\ ly573144\h8h_mc_laij \final\data\observed\shared\ | |
| | TFLs: (ME2 addendum locks) | Lilly Statistics | Test transfers after global cohort final lock and before ME2 addendum lock | \lillyce\qa\ ly573144\h8h_mc_laij \miscx\output\shared<br>x starts a 4 and goes for as many country locks as needed | |
| Unblinded for both global cohort and ME2 cohort(s) | Raw data: All | inVentiv Global_DSS_CDTS | ME2 addendum lock | \lillyce\prd\ ly573144\h8h_mc_laij \miscx\data\raw\shared<br>x starts a 4 and goes for as many country locks as needed | Sources: IWRS |
| | SDTM: All | Lilly Statistics | ME2 addendum lock | \lillyce\prd\ ly573144\h8h_mc_laij \miscx\data\observed\shared<br>x starts a 4 and goes for as many country locks as needed | |
| | ADaM: All | Lilly Statistics | ME2 addendum lock | \lillyce\prd\ ly573144\h8h_mc_laij \miscx\data\analysis\shared<br>x starts a 4 and goes for as many country locks as needed | |
| | TFLs: | Lilly Statistics | ME2 addendum lock | \lillyce\prd\ ly573144\h8h_mc_laij \miscx\output\shared<br>x starts a 4 and goes for as many country locks as needed | |

Abbreviations: ADaM = analysis data model;DSUR = development safety update report; GLS = Generic Lab System; IWRS = interactive web-response system; ME2 = maximized extended enrollment; SDTM = standard data tabulation model; TFLs = tables, figures, and listings; TLSRs = trial-level safety reviews.

Note: ***mmm*** and ***yyyy*** indicate the month and year of DSUR or other regulatory transfers; ***n*** indicates the sequence number of TLSR.

[a] The personnel in the function to deliver data will have access in CLUWE to check containers before transfer.

**Leo Document ID = 134dbeac-7fd8-4661-9f00-6d84fee34559**

**Approver:** PPD

**Approval Date & Time: 23-Jul-2020 13:49:49 GMT**

**Signature meaning: Approved**