LAIH SAP v2

Randomized, Double-blind, Placebo Controlled Trial of Lasmiditan in a Single Migraine Attack in Japanese Patients Suffering from Migraine With or Without Aura – the MONONOFU Study

NCT03962738

Approval Date: 08-Jul-2020

1. Statistical Analysis Plan: H8H-JE-LAIH: RandoMized, DOuble-bliNd, PlacebO-coNtrolled Trial Of Lasmiditan in a Single Migraine Attack in Japanese Patients SuFfering from Migraine With or WithoUt Aura – the MONONOFU study

Confidential Information

Lasmiditan (LY573144)

Study H8H-JE-LAIH (LAIH) is the bridging trial to the Phase 3 Study 302/LAHK (SPARTAN), with dose-response in efficacy of lasmiditan in the range of 50-200 mg. Study LAIH assesses the efficacy and safety of lasmiditan in acute treatment of a migraine attack in Japanese adult patients with or without aura.

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H8H-JE-LAIH

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

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3. Revision History

The Statistical Analysis Plan (SAP) Version 1 was approved prior to first patient visit (FPV) and any unblinding of the study team. Version 2 was approved prior to the database lock (unblinding).
The following topics were major updates from SAP version 1. Minor updates (e.g. clarification of definitions, and adding listings, adding examples for clarification, adding the same analysis with different population) were not listed in general.

- Sec. 5.3 (Population for Analyses): In Table LAIH. 5.2, definitions of ITT and mITT were updated with "Patients will be evaluated by the drug to which they are randomized".
- Sec. 5.3 (Population for Analyses): Condition [C0] was added for clarification purpose. It was originally specified in Table LAIH. 5.2.
- Sec. 5.3 (Population for Analyses): Condition "[C2] Baseline measurement in eDiary is BEFORE the dosing" was deleted. Eventually, [C3] and [C4] become [C2] and [C3], respectively. This method was used in the Study COL MIG-302/H8H-MC-LAHK. (SPARTAN) which was the bridging target study for this study.
- CCI [redacted]
- Sec. 5.4 (General Statistical Considerations): ANCOVA was changed to ANOVA. Analysis method was specified (LSMeans).
- Sec. 5.4 (General Statistical Considerations): For safety analyses, 5 treatment groups (PLA, LY50, LY100, LY200, LY_ALL) would be used. Originally, it was 4 treatment groups (PLA, LY50, LY100, LY200).
- Sec. 5.4 (General Statistical Considerations): For demographics, 6 treatment groups (PLA, LY50, LY100, LY200, LY_ALL, Overall) would be used. Originally, it was 5 treatment groups (PLA, LY50, LY100, LY200, Overall).
- Sec. 5.4 (General Statistical Considerations): For clarification in Kaplan-Meier method, analysis detail was specified.
- Sec. 5.4 (General Statistical Considerations): To use data from CRF instead of IWRS for statistical models, the text was revised as "When baseline usage of **preventive** medications to reduce the frequency of migraine (Yes/No) is included in a statistical model, it is based on CRF, not IWRS".
- Sec. 5.4 (General Statistical Considerations): Clarification was added "Efficacy analyses are based on eDiary data."
- Sec. 5.4 (General Statistical Considerations): Definition of comorbid condition was added.
- Sec. 5.4 (General Statistical Considerations): For protocol deviation summary, analysis with ITT was added.

- Sec. 5.4 (General Statistical Considerations): For clarification, the text was updated as "Other efficacy and **health outcome** will be based on ITT."
- Sec. 5.4 (General Statistical Considerations): Analysis population for summary of medication and eDiary compliance were specified as safety population.
- Sec.5.4.1 (Handling of Missing Values): For pain free, Pain relief, and MBS analysis, the following was deleted: "If baseline is missing then all post-baseline measurements are considered as "non-responder" because there are no such patients due to eDiary structure.
- Sec.5.4.1 (Handling of Missing Values): The following was added, "if a patient takes a rescue/recurrent medication at some postbaseline timepoint (see Section 5.4), then all evaluation after that timepoint becomes nonresponder, even if the evaluation is missing."
- Sec.5.4.1 (Handling of Missing Values): Censoring methods for time-to-event analyses were clarified.
- Sec.5.4.2 (Derivation of eDiary Assessment Times for Efficacy and Exploratory Analysis): The following sentence is updated to handle contradicting data, "Unless otherwise specified, if incomplete data or contradictions are found for other reasons, then such data will not be used for analysis. Such irregular cases will be listed."
- Sec.5.5.1 (Patient Disposition): For readability and clarification, the section was updated. Detail is specified for each TFLs:
  - Summary of Discontinuation Before Randomization
  - Summary of Study Disposition
  - Listing of Study Disposition
  - Summary of Analysis Population
  - Listing of Analysis Population
  - Summary of Patient Allocation by Site
  - Listing of Study Disposition for COVID-19 related subjects (newly added analysis)

  "Summary of mITT population with headache severity data at both 0 hours and 2 hours post dose" was deleted.
- Sec.5.5.2 (Important Protocol Deviations): This section is simplified. Detailed definitions would be specified in Trial Issue Management Plan and individual patient record.
- Sec.5.5.3 (Patient Characteristics): Some of the contents are clarified and newly added, including details summary of prior triptan use. The cardiovascular risk factor (CVRF) definition is modified. Additional mTOQ analysis definition was specified.
- Sec.5.5.4 (Previous, Concomitant, and Post-Dose medications). For classification of medication, medical review would be necessary. It was added for clarification.
- Sec.5.5.5 (Compliance): Definition of compliance was clarified.

- Sec.5.5.6 (Treatment Dosing): The section was newly added.
- Sec.5.6.1 (Primary and Key Secondary Analysis): Estimation methods for [T1] and [T2] were added (Wald's test). An estimation method for response rate using logistic regression was added.
- Sec.5.6.1 (Primary and Key Secondary Analysis): "Summary of Characteristics of Treated Migraine (at onset of dosing)" was added.
- Sec.5.6.2 (Sensitivity Analysis): "Remove patients who took the dose with baseline mild severity in mITT population" was deleted because such patients would be excluded in mITT after modifying the mITT condition in SAP version 2.
- Sec.5.6.2 (Sensitivity Analysis): "Include patients who recorded the baseline measurement in eDiary after taking the dose and who has 2 hours assessment" was deleted because such patients would be included in mITT after modifying the mITT condition in SAP version 2.
- Sec.5.6.2 (Sensitivity Analysis): [T1] specific sensitivity analysis was added. Estimation methods for response rate using logistic regression was added.
- CCI [redacted]
- Sec. 5.6.3 (Details of Efficacy Analyses): For Disability and PGI-C analysis, summary table will be created.
- Sec. 5.6.3 (Details of Efficacy Analyses): The name of the analysis "Incidence of Headache Recurrence Through 48 Hours Post-Dose" was modified to "Incidence of Headache Recurrence Through 24/48 Hours Post-Dose." The definition of missing data case was added.
- Sec. 5.6.3 (Details of Efficacy Analyses): The definition and analysis of "Summary of Symptom-Free at Assessment Times (Nausea, Phonophobia, Photophobia, Vomiting)" (ID=17) was added.
- Sec. 5.6.3 (Details of Efficacy Analyses): In Table LAIH. 5.3, for "Time to Meaningful Pain Relief Through 48 Hours" and "Time to Pain Free Through 48 Hours", 6 hours and 8 hours results were added.
- Sec. 5.6.3 (Details of Efficacy Analyses): Following analyses were deleted because they would be less important.
  - Relative migraine freedom (original ID=17)
  - EQ-5D-5L responder analysis (original ID=22)
  - Pain Relief at 24 Hours and 48 Hours with Pain Relief at 2 Hours (original ID= 27)
  - Pain Free at 24 Hours and 48 Hours with Pain Relief at 2 Hours (original ID= 28)

- Sec. 5.6.3 (Details of Efficacy Analyses): Modified sustained pain freedom: The definition of missing data is modified to align with other historical data of triptans. In the new definition, if the data is missing, then it is excluded from the responder analysis instead of setting it as non-responder.
- Sec. 5.6.3 (Details of Efficacy Analyses): For Treatment Satisfaction, "Distribution of responses and proportion of patients with agree or strongly agree" was added.
- Sec. 5.6.3 (Details of Efficacy Analyses): In Table LAIH. 5.3, ANCOVA was changed to ANOVA because ANOVA was the actual method for analyses.
- Sec. 5.6.3 (Details of Efficacy Analyses): Figures for ratio of achieving Pain Free, Pain Relief, and MBS-free, MBS-Free by Chosen Symptom up to 2 hours were added.
- Sec.5.7.1 (Adverse Events): "AEs" were explicitly defined as "AEs are collected from Visit 1 to Visit 3."
- Sec.5.7.1 (Adverse Events): "Post-dose AEs" were defined as the same as the TEAE except without the restriction of the 48 hours cutoff after the dosing. In addition, its TFLs would be created.
- Sec. 5.7.1 (Adverse Events): "By PT by decreasing frequency with an incidence in any lasmiditan group ≥1.5% and greater than placebo" was changed to "By PT by decreasing frequency with an incidence in any lasmiditan group ≥1.5% and PT including "Vertigo."" CCI [redacted]
- Sec.5.7.1 (Adverse Events): (AE): From "overview of AEs", total number of events is deleted because it would not be used in CSR. "Pot-dose AEs" is added.
- Sec.5.7.3 (Vital Signs and Weights): The wording "treatment emergent" was deleted because by nature, Vital Signs and weights were measured at Visit 3 which were beyond 48 hours from dosing, in general.
- Sec.5.7.3 (Vital Signs and Weights): BMI was added.
- Sec.5.7.4 (Laboratory Tests): The wording "treatment emergent" was deleted because by nature, lab tests were taken at Visit 3 which were beyond 48 hours from dosing, in general.
- Sec.5.7.4 (Laboratory Tests): Both standard and conventional units' outputs for continuous analysis were specified.
- Sec.5.7.7 (Safety Topics of Interest): This section was newly added. CCI [redacted]
- Sec.5.8 (Subgroup Analysis): The analysis "Patients who fail the most recent triptan at any time before screening" was renamed as "Triptan responder vs. insufficient responder (based on the most recent triptan experience)" to clarify the definition (subgroup ID= SUB1).
- Sec. 5.8 (Subgroup Analysis): "Patients with one or more CVRF" was updated as "Patients with two or more CVRF" (subgroup ID= SUB12).
- Sec. 5.8 (Subgroup Analysis): New subgroup definitions and analyses were added. The entire subgroup analysis was summarized in Table LAIH. 5.6.

- Sec. 5.8 (Subgroup Analysis): Analysis methods and statistical models were specified.

4. Study Objectives

4.1. Primary Objective

The primary efficacy objective is to evaluate the efficacy of lasmiditan 200 mg on migraine headache pain freedom compared to placebo in Japanese adult patients suffering from migraine with or without aura. It is measured by the proportion of patients in each group who are pain free (defined as moderate or severe headache pain becoming none) at 2 hours postdose during the attack.

4.2. Key Secondary Objectives

There are two key secondary objectives:

- To evaluate the dose response of lasmiditan 200 mg, 100 mg, and 50 mg on migraine headache pain freedom compared to placebo. It is measured by the proportion of patients in each group who are pain free at 2 hours postdose during the attack.
- To evaluate the efficacy of lasmiditan 100 mg on migraine headache pain relief compared to placebo. It is measured by the proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none) in each group at 2 hours postdose during the attack.

4.3. Objectives and Endpoints

Table LAIH. 4.1 summarize the primary, two key secondary, other secondary objectives and endpoints. The complete list of the exploratory objectives is in Section 5.6.3.

Table LAIH. 4.1 Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the efficacy of lasmiditan 200 mg on migraine headache pain freedom compared to placebo in Japanese adult patients suffering from migraine with or without aura.	The proportion of patients in each group who are pain free (defined as moderate or severe headache pain becoming none) at 2 hours postdose during the attack.
Key Secondary	
• To evaluate the dose response of lasmiditan 200 mg, 100 mg, and 50 mg on migraine headache pain freedom compared to placebo • To evaluate the efficacy of lasmiditan 100 mg on migraine headache pain relief compared to placebo	• The proportion of patients in each group who are pain free at 2 hours postdose during the attack • The proportion of patients with pain relief (defined as moderate or severe headache pain becoming mild or none) in each group at 2 hours postdose during the attack
Other Secondary	
• To evaluate the efficacy of lasmiditan 100 mg and 50 mg on migraine headache pain freedom compared to placebo	• The proportion of patients in each group who are pain free at 2 hours postdose during the attack

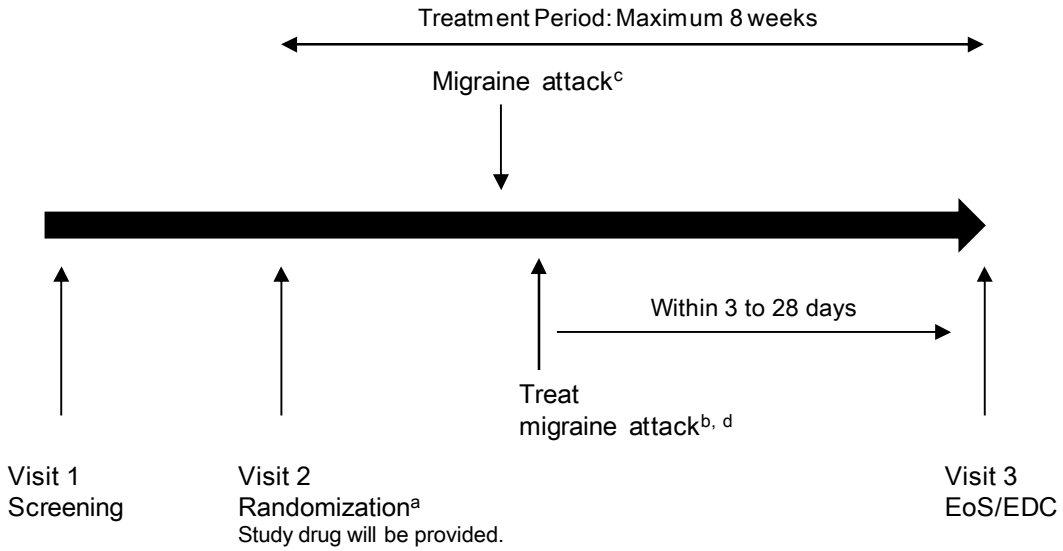
Objectives	Endpoints
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on freedom from MBS compared to placebo	• The proportion of patients in each group who are free of MBS associated with migraine at 2 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg and 50 mg on pain relief compared to placebo	• The proportion of patients with pain relief in each group at 2 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on sustained freedom from pain compared to placebo	• The proportion of patients in each group with 24-hour and 48-hour sustained pain freedom during the attack defined as pain free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg at 2 hours on freedom from symptoms associated with migraine compared to placebo	• The proportion of patients in each group that are free of symptoms associated with migraine at 2 hours postdose during the attack, including each of the following: phonophobia, photophobia, nausea, and vomiting
• To explore the time course of lasmiditan 200 mg, 100 mg, and 50 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 after taking the dose of study drug during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 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 attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on health utility compared to placebo	• Mean change from baseline in utility in each group as measured by the EuroQol 5 dimension 5-level scale (EQ-5D-5L), at 24 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 50 mg, and 100 mg on Patient Global Impression of Change (PGI-C) compared to placebo	• The proportion of patients in each group very much or much better as measured by PGI-C, at 2 and 24 hours postdose during the attack
• To evaluate the efficacy of lasmiditan 200 mg, 100 mg, and 50 mg on Health-Related Quality of Life (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 Migraine Quality of Life Questionnaire (MQoLQ), in each group at 24 hours postdose of study during the attack

Abbreviations: 24-hour MQoLQ = 24-Hour Migraine Quality of Life Questionnaire; EQ-5D-5L = EuroQol 5-dimension 5-level scale; HRQoL = Health-Related Quality of Life; MBS = the most bothersome symptom as identified by the individual from the associated symptoms of nausea, phonophobia or photophobia; PGI-C = Patient Global Impression of Change; HRQoL = Health-Related Quality of Life; MQoLQ = Migraine Quality of Life Questionnaire.

5. A Priori Statistical Methods

5.1. Study Design

Figure LAIH. 5.1 shows the study design. Appendix 1 shows efficacy assessment timing in eDiary after Visit 2.



Abbreviations: EDC = early discontinuation; EoS = end of study.

a Preventive treatment allowed (if stable 3 months prior to Visit 1).

b Patients will take 3 tablets to maintain blinding.

c Patients will wait to take study drug until migraine pain is moderate/severe; must be the FIRST treatment for the migraine taken within 4 hours of pain onset.

d Patients who do not treat a migraine with study drug should attend Visit 3 at 8 weeks after Visit 2. Visit 3 should be finished by 8 weeks (+14 days as visit allowance) after Visit 2.

Figure LAIH. 5.1 Patient flow overview Clinical Protocol H8H-JE-LAIH.

5.2. Sample Size Determination

Approximately 1157 patients will be screened to achieve approximately 880 patients randomized, and approximately 624 patients with data for a migraine attack.

Table LAIH. 5.1 illustrates the power calculation.

The power calculation is based on the results of the Study SPARTAN*. The primary endpoint (headache pain free at 2 hours postdose) results in SPARTAN were 21.3%, 28.6%, 31.4%, and 38.8% for placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg, respectively, and the rates of headache pain relief at 2 hours postdose were 47.7%, 59.0%, 64.8%, and 65.0% for placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg, respectively.

To ensure sufficient total statistical power for the primary and two key secondary analyses, the number of randomized patients will be set at 880. Considering 29% dropout rate, this sample size has 85.6% power. More specifically, the study will include:

- Number of screened patients = 1157.
- Number of randomized patients = 880 (= 1157*0.76, approximately 24% screen failure based on assumptions from LAIJ***), with [placebo:lasmiditan 50 mg:lasmiditan 100 mg:lasmiditan 200 mg] = 268:114:268:230 (7:3:7:6 ratio) for the attack.
- Number of patients who have a migraine attack = 624 (= 880*0.71, approximately 29% of patients would not dose to treat a migraine attack during the 8 week period based on SPARTAN/SAMURAI**), with [placebo:lasmiditan 50 mg:lasmiditan 100 mg:lasmiditan 200 mg] = 190:81:190:163 (7:3:7:6 ratio).

Note*: SPARTAN is the Study COL MIG-302/H8H-MC-LAHK.

Note**: SAMURAI is the Study COL MIG-301/H8H-MC-LAHJ.

Note***: LAIJ is the Study H8H-MC-LAIJ.

Note: The power is calculated based on simulation. In the simulation, the correlation between pain free and pain relief was assumed to be zero which would result in a conservative power.

Table LAIH. 5.1 Study Power Calculation

	Arm	**N**
Arm and number of patients	PLA	190
	LY50	81
	LY100	190
	LY200	163
	Total	624
Power	Primary [T1] : PLA vs LY200 = 93.6% (2 sided, alpha = 0.05) Key secondary [T2]: CA (PLA,LY50,LY100,LY200) = 94.9% (2 sided, alpha = 0.05) Key secondary [T3]: PLA vs LY100 = 91.2% (2 sided, alpha = 0.05) Total (primary and two key secondaries) = 85.6%	
Primary endpoint/Key secondary endpoints	[T1] and [T2]: Pain free at 2 hours postdose [T3]: Pain relief at 2 hours postdose	

Abbreviations: alpha = type 1 error; CA = Cochran Armitage trend test; LY200 = lasmiditan 200 mg; LY100 = lasmiditan 100 mg; LY50 = lasmiditan 50 mg; PLA = placebo; N = number of patients for the corresponding arms which correspond to modified ITT (mITT) population; [T1], [T2], and [T3] are defined in Section 5.6.1.

In this document, we use the arm abbreviations as PLA = placebo, LY50 = lasmiditan 50 mg, LY100 = lasmiditan 100 mg, and LY200 = lasmiditan 200 mg. In addition, LY_ALL (combination of LY50, LY100, and LY200) and Overall (combination of PLA and LY_ALL) will be used.

5.3. Populations for Analyses

For purposes of analysis, the following populations are defined. Patients in all these populations will be evaluated by the drug to which they were randomized except the safety population (Table LAIH. 5.2).

Table LAIH. 5.2 Populations for Analyses

Population	Description
All enrolled population	All participants who sign informed consent
All randomized population	All randomized patients
ITT population	All randomized patients who use at least 1 dose of study drug and have any postdose headache severity or symptom assessments. Patients will be evaluated by the drug to which they are randomized
mITT population	All ITT patients who treat a migraine attack within 4 hours of onset. The mITT population will be the primary analysis population. Patients will be evaluated by the drug to which they are randomized
Per Protocol Set (PPS)	All mITT patients will be considered PPS if they do not have major protocol deviations which might impact the assessment of efficacy. Details are specified in Section 5.5.2.
Safety Population (SP)	All randomized patients who use at least 1 dose of study drug, regardless of whether they underwent any study assessments. Patients will be evaluated by the drug they use, not by the drug to which they are randomized

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

To be more precise, patients in mITT and ITT population must satisfy all of the following conditions,

Condition of mITT population: [C0], [C1], [C2] and [C3],

Condition of ITT population: [C0], [C1] and [C2],

where

[C0] At least one postdose headache severity or symptom assessment exists

[C1] Dosing time is recorded in eDiary

[C2] Baseline migraine severity is moderate, or severe.

[C3] Dosing time is within 4 hours of the migraine attack

[C1] is necessary because eDiary is the data source in which we capture all efficacy information including their evaluation timing. The dosing time becomes the onset time of all of the following efficacy data.

[C2] is to eliminate patients with migraine severity mild or none.

5.4. General Statistical Considerations

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

In general, we will use the following statistical methods unless otherwise specified. For detailed definitions of [T1] (primary objectives), [T2] and [T3] (2 key secondary objectives), see Section 5.6.1:

- For efficacy analyses based on proportion, the logistic regression used in [T1] will be applied. The model term includes treatment and baseline usage of preventive medications to reduce the frequency of migraine (Yes/No).
- When treatment group (PLA, LY50, LY100, LY200) is in a statistical model, it will be regarded as a categorical variable.
- For analysis based on continuous variable (change from baseline), if analysis of variance (ANOVA) is used then its covariate includes treatment and baseline usage of preventive medications to reduce the frequency of migraine (Yes/No). LSMeans will be used for estimation.
- For safety analyses and demographics, only descriptive statistics will be presented, and no statistical test will be conducted.
- Statistical tests will be conducted at a 2-sided significance level of 0.05. The 95% confidence interval will be presented if appropriate.
- No multiplicity adjustment for multiple tests (between the arms for the same efficacy objective, nor between the different objectives for the same arms) will be made except primary and two key secondary analyses ([T1], [T2], and [T3]).
- Analyses will be reported by 4 treatment groups (PLA, LY50, LY100, LY200) in general.
- Frequency tables such as those for AE or TEAEs will be sorted by LY_ALL, in decreasing frequency.
- For safety, 5 treatment groups (PLA, LY50, LY100, LY200, LY_ALL) will be displayed.
- For demographics, 6 treatment groups (PLA, LY50, LY100, LY200, LY_ALL, Overall) will be displayed. Here “Overall” means all combined arms (PLA + LY_ALL).
- For efficacy analyses based on proportions, odds ratio along with 95 % confidence interval will be calculated at 2 hours post-dose time point (each treatment vs. placebo).

- When Cochran-Mantel-Haenszel test is used for a multi-category response, baseline usage of preventive medications to reduce the frequency of migraine (Yes/No) is used for stratification (each treatment vs. placebo).
- For Kaplan-Meier analysis, corresponding figures will be created. Quartiles and rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.
- When baseline usage of preventive medications to reduce the frequency of migraine (Yes/No) is included in a statistical model, it is based on CRF, not IWRS.
- Efficacy analyses are based on eDiary data, unless otherwise specified.
- Comorbid condition is based on Visit 1.
- When median is used for subgroup analysis (e.g. SUB4, body weight), the median is based on mITT population.

We will use the following analysis population rules unless otherwise specified (see population definitions in Section 5.3):

- Protocol deviation summary will be based on all randomized and mITT/ITT.
- Demographics and Baseline characteristics will be based on mITT/ITT/safety population (SP).
- Efficacy analyses [T1], [T2], [T3], and MBS will be based on mITT/ITT/per-protocol set (PPS).
- Other efficacy and health outcome will be based on ITT.
- Safety analyses (e.g., AE, laboratory assessments/vital signs), medication, and treatment compliance/eDiary compliance will be based on SP.

When continuous variables, including change from baseline scores, is summarized using descriptive statistics, it will show 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 and median will be presented to one more decimal place than the raw data. Standard deviation will be presented to two more decimal places than the raw data. P-values will be presented to three 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.

Observations collected prior to dosing will serve to determine a baseline measurement; the latest available measurement prior to dosing will be used as the baseline. For data collected by eDiary, the baseline values will be the Hour-0 assessment times identified in the eDiary.

SAS® software (version 9.2 or higher) will be used to perform most or all statistical analyses.

Patients and subjects are used interchangeably in this document.

5.4.1. Handling of Missing Values

Subjects who fail to record information at an analysis time point will have that value considered missing in the respective table (hence, no imputation), unless otherwise specified.

Pain free, Pain relief, and MBS analysis are exceptions to this. Missing value at a particular time point is considered as "non-responder."

Note that if a patient takes a rescue/recurrent medication at some postbaseline timepoint (see Section 5.4), then all evaluation after that timepoint becomes nonresponder, even if the evaluation is missing.

For time-to-event analyses (Time to Meaningful Pain Relief Through 48 Hours, Time to Pain Free Through 48 Hours), patients will be censored at the first time when rescue/recurrent medication are used or at 48 hours, whichever the earliest.

For the other time-to-event analyses (Kaplan-Meier analyses), the patient will be censored at the first missing evaluation time point or rescue/recurrent medication taken time (postbaseline), or the last possible evaluation point whichever the earliest, unless otherwise specified. For example, the last possible evaluation point of disability is at 24 hours.

A sensitivity analysis for missing data will be performed. (See Section 5.6.2).

5.4.2. Derivation of eDiary Assessment Times for Efficacy and Exploratory Analysis

There will be some scenarios whereby responses appear to have been limited by the diary programming if questions are not answered during the programmed window.

One specific scenario is missing dose timing data. If the dose is reported taken in the CRF but the subject is not able to select the date and time in the diary, then the date of dose will be missing in diary data. In such cases, efficacy assessments will be considered as missing. However, for safety analysis, the dosing date and time in the CRF will be considered as the baseline timing.

Unless otherwise specified, if incomplete data or contradictions are found for other reasons, then such data will not be used for analysis. Such irregular cases will be listed.

e.g. If meaningful pain free time is before dosing time, then it is contradiction. This data will not be used for the meaningful pain free time analysis.

e.g. If there are two data record at a specific timepoint, then first data record is used for that time point and the other one will be discarded. In addition, all data recorded at subsequent timepoints will be discarded.

5.5. Treatment Group Comparability

5.5.1. Patient Disposition

The following summary and listing will be created

Summary of Discontinuation Before Randomization

Reason for screen failure will be presented (by overall). Display count and percentage with respect to the screen failed patients.

Summary of Study Disposition

It is summarized by overall (total of PLA/LY50/LY100/LY200), by LY_ALL (total of LY50/LY100/LY200) and by treatment groups (PLA/LY50/LY100/LY200) as counts. The analysis population is all randomized patients/SP/ITT/mITT. The summary will be created for each analysis population separately. The summary will display the number of subjects in each category/sub-category/sub-sub-category. For both category and sub-categories, display count and percentage with respect to the number of subjects in the direct root category. (E.g. The direct root of a sub-sub-category is the sub-category.):

- Subjects who completed the study
  - Subjects who took study treatment
  - Subjects who did not take study treatment
    - Reasons for not treated (by treatment/overall).

- Subjects who discontinue the study
  - Reasons for the study discontinuation (including lost-to-follow-up).

Note 1: A patient who completes the study is one who is randomized and does not discontinue throughout the 8 weeks treatment period, regardless of study drug administration.

Note 2: All subjects who discontinue the study do not take study treatment.

Listing of Study Disposition

Disposition data and subjects who discontinue from the study will be presented per subjects for enrolled population

Summary of Analysis Population

The summary contains following counts. It is summarized by overall (total of PLA/LY50/LY100/LY200) and by treatment group (PLA/LY50/LY100/LY200) as counts.

- The number of screened patients. (all enrolled population)
- Subjects in each of the analysis population, all randomized population/ITT/mITT/SP/PPS (by treatment/overall). Display count and percentage with respect to all randomized population.

Listing of Analysis Population

For each patient, display Yes/No flags for Enrolled Population, all randomized population/ITT/mITT/SP/PPS.

In addition to the summary information, the listing contains "reasons for excluding from PPS".

Summary of Patient Allocation by site

For each site, counts enrolled population/all randomized population/SP/ITT/mITT/PPS.

Listing of Study Disposition for COVID-19 related subjects

The listing for subjects who discontinued due to COVID=19 will be created for enrolled population.

5.5.2. Important Protocol Deviations

Listings of subjects with important protocol deviations will be provided for all randomized population. Important protocol deviations will be determined before unblinding. Detailed criteria and identification methods will be specified in separate document (Trial Issue Management Plan and individual patient record) which also specifies exclusion of PPS.

Summary of important protocol deviations will be created for all randomized population/ITT/mITT (by treatment/overall)

5.5.3. Patient Characteristics

Patient characteristics will be summarized by 6 treatment groups (PLA, LY50, LY100, LY200, LY_ALL, Overall). Summaries will include descriptive statistics for continuous measures and for categorical measures.

- Demographic (age, gender, race, height, weight, and body mass index)

Note: Age (years) will be calculated as (Informed Consent Date - 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 because only birth year is collected through eCRF.

- Migraine history
  - Number of headache days subjects experience 3 months prior to informed consent

  - Number of days subjects take triptan for migraine 3 months prior to informed consent
  - Duration of migraine history:

    Note: It is calculated as (Informed Consent Date - Date of Migraine Diagnosis + 1)/365.25.
  - Experienced Migraines with and without aura
  - Average number of migraine episode (migraine attacks) per month 3 months prior to informed consent
- MIDAS at Baseline (total score and each score)
- Medical history and Pre-existing condition (specified in Section 5.5.3.1)
- Frequency of Cardiovascular Risk Factor (CVRF) by each factor (defined in Section 5.8)
- Medical history of special interest for the subject's first-degree relatives and second-degree relatives defined as:
  - Coronary artery disease
  - Cardiovascular disorder
  - Cerebrovascular disorder
  - Migraine
- Alcohol usage (never/current/former)
- Tobacco usage (never/current/former)
- Female reproductive status (Yes/No) for female only
- Employment Status (Keeping House/Self-employed/Student/Working for pay/Other)
- Summary of mTOQ-6 for each question

The baseline mTOQ-6 is summarized in two ways:

[mTOQ-6 Conversion Method 1] Convert responses as follows: Never (1); Rarely (2); Less than half the time (3); Half the time or more (4), producing a range of total scores from 1 to 24. (This method is specified in LAIH PROTOCOL.)

[mTOQ-6 Conversion Method 2] Convert responses as follows: Never (0 points); Rarely (0 points); Less than half the time (1 points); and Half the time or more (2 points). A total score from 0 to 8 is calculated by summing the points from 4 of the items (2-hour pain free, sustained 24-hour pain relief, comfortable to make plans, and perceived control) which define categories of acute treatment response: very poor (0), poor (1-5), moderate (6-7), and maximum (8) treatment efficacy (Lipton et al. 2015).

Note: If patient has missing response, then it will be excluded from the summary for that question.

- Summary of EQ-5D-5L of each question, index score and visual analog scale (Visit 2)
- Summary of Driving Assessment at Baseline:
  - Driving assessment (Yes/No)

    Note: "Yes" means patient who has a driver's license at Visit 2. "No" means patient who does not.
  - Involvement in any car accidents in past 6 months (yes and being the driver/otherwise)
  - If anyone involved in that accident have to seek medical attention for injury
  - If the subject has a migraine prior to or during the accident
  - If the subject has taken any medications to treat his migraine prior to the accident
  - Received any citations/tickets for any moving violations (Yes/No). If Yes, display the reason:
    - speeding violation,
    - failure to stop
    - disregarding traffic light
    - failure to signal
    - seat belt violation
    - cell phone related violation
    - violation of rules around school buses and school zone
    - falling asleep while driving
    - driving under the influence
    - other
  - If the subject has a migraine prior to or during the traffic violation
  - If the subject has taken any medications to treat his migraine prior to the violation
  - Narrative for the car accident for all patients will be created as listing.

All demographic data above will be presented in a listing for safety population.

In addition, a detailed summary of triptan usage at baseline will be created. It is defined in "Triptan responder vs. insufficient responder (SUB1)" in Section 5.8.

5.5.3.1. Pre-Existing Conditions and Medical History

Medical history and pre-existing conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) with the latest version 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 system organ class and preferred term. All pre-existing conditions and medical history will be presented in a listing.

5.5.4. Previous, Concomitant, and Post-Dose medications

The frequency and percentage of prior, concomitant, and post-dose medication use will be presented by treatment group.

- Prior medications are those taken (started) before study drug dosing.
- Concomitant medications are those taken within 48 hours (inclusive) after study drug dosing.
- Post-dose medications are those taken after 48 hours (exclusive) of study drug dosing and on or before the end of the study.

Prior/Concomitant medications/Post-dose are summarized in 3 groups:

[1] Acute migraine treatments

[2] Preventive migraine treatments

[3] The other medications (medications which are not categorized in [1] nor [2])

These are presented by ATC4 medication class and WHO drug name. Medications will be coded using the WHO Drug Dictionary with the latest version and sorted by frequency of preferred name. [1] and [2] are defined in a separate EXCEL by medical review.

The descriptive statistics of the indications, the responses, and the discontinuation reasons will also be presented for prior medications [1] and [2] displayed by treatment and overall.

Listing of Migraine Treatments Used in the Past Three Months will be created for safety population.

5.5.5. Compliance

Treatment compliance will be assessed in terms of the actual dose. Treatment compliance will be used to characterize the patients and determine clinical evaluability for some analyses. Treatment compliance will be summarized by descriptive statistics (counts for each category of treatment compliance=yes/no, and their percentage (%)) (by treatment/overall). This is based on Safety Population. If patients took all assigned dose (measured by the amount of returned tablet), then his compliance=yes. Otherwise his compliance=no.

The list of treatment compliance will be created (Dispense Date, # of tablets dispensed, Returned Date, # of tablets returned, compliance (%), lot number)

Electronic diary compliance (entered or missing) at each time point will be summarized (by treatment/overall)

The list of the eDiary compliance will be created.

5.5.6. Treatment Dosing

Summary of Migraine Onset and Dosing Times (frequency cross table) will be created by 6 treatment groups (PLA, LY50, LY100, LY200, LY_ALL, Overall).

Migraine onset time is categorized as midnight -3AM/3AM-6AM/6AM-9AM/9AM-Noon/Noon-3PM/3PM-6PM/6PM-9PM/9PM-Midnight/Total Dose time is categorized in the same way as the migraine onset time.

5.6. Efficacy Analyses

5.6.1. Primary and Key Secondary Analysis

The following statistical tests [T1] (primary), [T2] (key secondary), and [T3] (key secondary) will be conducted sequentially ([T1], [T2], then [T3]) by a gatekeeping method. This guarantees that the overall type 1 error across the set of primary and key secondary hypothesis tests is 0.05. Other assessments will not be part of the gatekeeping procedure.

- [T1] Primary: placebo vs. lasmiditan 200 mg (pain free at 2 hours) will be based on Wald's test by logistic regression.
- [T2] Key secondary: dose response of placebo, lasmiditan 50 mg, 100 mg, and 200 mg (pain free at 2 hours) will be based on Cochran-Armitage trend test.
- [T3] Key secondary: placebo vs. lasmiditan 100 mg (pain relief at 2 hours) will be based on Wald's test by logistic regression.

The analysis population for [T1], [T2], and [T3] under the gatekeeping procedure is the mITT.

When testing sequentially ([T1], [T2], and [T3]), if one of them becomes statistically non-significant, then all subsequent analyses will be conducted but will be designated as exploratory rather than confirmatory. That means, if [T1] is not significant, then [T2] and [T3] are exploratory. If [T1] is significant but not [T2], then [T3] is exploratory.

Note that regardless of the test results in [T1], [T2], and [T3], the other secondary and exploratory analysis are not adjusted in multiplicity (Section 5.6.4).

For the [T1] analysis, the statistical test will be based on placebo vs. lasmiditan 200 mg using the logistic regression model that includes treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and baseline usage of preventive medications to reduce the frequency of migraine (Yes/No).

For the [T2] analysis, the Cochran-Armitage trend test will be based on placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg. The trend parameter is 0, 50, 100, and 200. This is to estimate the dose-response relationship of lasmiditan (dose zero to 200mg).

For the [T3] analysis, the statistical test will be based on placebo vs. lasmiditan 100 mg using the logistic regression model that includes treatment (placebo, lasmiditan 50 mg, lasmiditan 100 mg, and lasmiditan 200 mg) and baseline usage of preventive medications to reduce the frequency of migraine (Yes/No).

A sample SAS code for logistic regression is;

```
proc logistic data = myData;
  class TRT(param=ref ref="PL") baseMedUse;
  model AVAL(event='1') = TRT baseMedUse;
run;
```

To estimate the response rate for each arm, along with 95% confidence interval, least-square means (LSMeans) will be used.

Summary of Characteristics of Treated Migraine (at onset of dosing) will be created (mITT/SP).

Listing of Subject Efficacy Responses will be created.

5.6.2. Sensitivity Analysis

As sensitivity analysis for [T1] (primary), [T2], [T3] (key secondary), and MBS, following method will be conducted:

- The same analysis will be conducted based on ITT and PPS
- "non-responder" patients due to missing data (post baseline) will be excluded from (Reference Section 5.4.1) mITT population

In addition, [T1] [T3] analysis will be conducted for patients who are in mITT and who have not vomited up to 2 hours. That is, eliminate patients who recorded vomiting at least once between 0 hour to 2 hours (inclusive), recorded in the eDiary.

In addition, as sensitivity analysis for [T1], separate subgroup models specified below will be fitted:

[1] Previous triptan response (none + poor (0-1), good (2-3))

[2] Baseline disability severity (`need complete bed rest`, the others)

[3] Baseline headache severity (moderate or severe)

[4] Baseline associate symptom (with/without nausea)

[5] Menstrual period (-2d before cycle to total 5 days)

[6] Body weight (continuous variable)

[7] Age (continuous variable)

[8] Gender

[9] Baseline migraine attacks (<=5 attacks per month, > 5 attacks per month)

[10] Time of dose relative to onset of migraine (dosing time <= 1 hour, dosing time > 1 hour)

[11] Duration of migraine history (<=median, > median)

The definition of [1] and [5] are the same as the one specified in Section 5.8.

The model term include treatment, baseline usage of preventive medications to reduce the frequency of migraine (Yes/No), subgroup, and treatment-by-subgroup interaction.

The response rate for each arm, along with 95% confidence interval, will be estimated based on LSMeans.

5.6.3. Details of Efficacy Analyses

Table LAIH. 5.3 is the list of primary/ key secondary/ other secondary/ exploratory analysis with each analysis population, timeframe and analysis method.

Table LAIH. 5.3 Primary, Key Secondary, Other Secondary and Exploratory Efficacy Variables and Analysis Methods

ID	Type	efficacy variables	POP	Timeframe	Analysis
1	PRIM /2ND	Headache Pain Free	mITT/ ITT/ PPS	up to 48h	LOGISTIC
2	2KEY	Pain Free Trend Test	mITT/ ITT/ PPS	2h	CA
3	2KEY /2ND	Headache Pain Relief	mITT/ ITT/ PPS	up to 48h	LOGISTIC
4	2ND	MBS-Free	mITT/ ITT/ PPS	up to 48h	LOGISTIC
5	2ND	Migraine Symptoms Present at Assessment Times (Nausea, Phonophobia, Photophobia, Vomiting)	ITT	up to 48h	LOGISTIC
6	OTH	MBS-Free by Chosen Symptom: (Nausea, Phonophobia, Photophobia)	ITT	up to 48h	LOGISTIC
7	2ND	Time to Headache Pain Free Through 48 Hours Post-Dose	ITT	up to 48h	KM
8	2ND	Time to Headache Pain Relief Through 48 Hours Post-Dose	ITT	up to 48h	KM
9	2ND	Time to MBS-Free Through 48 Hours Post-Dose	ITT	up to 48h	KM
10	OTH	Time to MBS-Free by Chosen Symptom Through 48 Hours Post-Dose: (Nausea, Phonophobia, Photophobia)	ITT	up to 48h	KM
11	2ND	Disability	ITT	0.5h/1h/2h/24h	LOGISTIC

12	OTH	Incidence of Rescue or Recurrence Medication Use	ITT	[0h-2h]/ [2h-24h]/ [24h-48h]	LOGISTIC
13	OTH	Incidence of Headache Recurrence Through 24/48 Hours Post-Dose	ITT	2h< recurrence <=24h 2h< recurrence <=48h	LOGISTIC
14	2ND	PGI-C	ITT	2h/24h	LOGISTIC
15	2ND	Sustained Pain Free at 24 Hours and 48 Hours	ITT	24h/48h	LOGISTIC
16	2ND	Time to No Disability Through 24 Hours	ITT	up to 24h	KM
17	OTH	Summary of Symptom-Free at Assessment Times (Nausea, Phonophobia, Photophobia, Vomiting)	ITT	up to 48h	LOGISTIC
18	OTH	Total Migraine Freedom	ITT	up to 48h	LOGISTIC
19	OTH	Modified Sustained Pain Free at 24 Hours and 48 Hours	ITT	24h/48h	LOGISTIC
20	OTH	Time to Meaningful Pain Relief Through 48 Hours	ITT	up to 48h (including 6h/8h)	KM
21	OTH	Time to Pain Free Through 48 Hours	ITT	up to 48h (including 6h/8h)	KM
22	2ND	Change from Baseline of EQ-5D-5L in Index Score	ITT	24h	ANOVA
23	2ND	Change From Baseline of EQ-5D-5L in Visual Analog Scale	ITT	24h	ANOVA
24	2ND	HRQoL Measured by MQoLQ in 5 Domains	ITT	24h	ANOVA
25	2ND	Treatment Satisfaction	ITT	48h	CMH

Abbreviations: 2KEY= key secondary analysis; 2ND = other secondary analysis; ANOVA= Analysis of Variance; CA= Cochran-Armitage trend test; CMH= Cochran-Mantel-Haenszel test; EQ-5D-5L = EuroQol 5-dimension 5-level scale; h= hour; HRQoL = Health-Related Quality of Life; ITT= intent-to-treat population ; KM= Kaplan-Meier analysis; LOGISTIC= logistic regression; MBS = the most bothersome symptom; MQoLQ = Migraine Quality of Life Questionnaire; mITT= modified intent-to-treat population; NA= not applicable (descriptive statistics is used); OTH= exploratory analysis; PGI-C = Patient Global Impression of Change; PPS= per protocol set population; PRIM= primary analysis

Definition of analysis used in Table LAIH. 5.3 are listed below:

Pain Free

It is defined as reduction in headache severity from moderate (2) or severe (3) at baseline to none (0) at indicated assessment time.

Pain Relief

It is definition as reduction in headache severity from moderate (2) or severe (3) at baseline to mild (1) or none (0).

MBS-Free

MBS-free is defined as the absence of the associated symptom of migraine (either nausea, phonophobia, or photophobia) at the indicated assessment time that was identified pre-dose as the most bothersome symptom. Subjects who record that no symptoms were present at time of dose are excluded from the MBS analysis.

Migraine Symptoms Present at Assessment Times (Nausea, Phonophobia, Photophobia, Vomiting)

This is 4 separate analysis of Nausea, Phonophobia, Photophobia, Vomiting, regardless of corresponding baseline values.

MBS-Free by Chosen Symptom: (Nausea, Phonophobia, Photophobia)

This is 3 separate subgroup analysis of MBS. For example, the nausea analysis is based on those who chose “nausea” as the most bothersome symptom at baseline.

Time to Headache Pain Free Through 48 Hours Post-Dose

It is defined as a reduction in headache severity to pain free at any assessment time for the first time through 48 hours after the dose.

Time to Headache Pain Relief Through 48 Hours Post-Dose

It is defined as a reduction in headache severity to pain relief at any assessment time for the first time through 48 hours after the dose.

Time to MBS-Free Through 48 Hours Post-Dose

It is defined as the absence of the associated symptom of migraine, (either nausea, phonophobia, or photophobia) that was identified pre-dose as the most bothersome symptom, at any assessment time for the first time through 48 hours after the dose.

Time to MBS-Free by Chosen Symptom Through 48 Hours Post-Dose: (Nausea, Phonophobia, Photophobia)

This is 3 separate subgroup analysis of “Time to MBS Free Through 48 Hours Post-Dose”. For example, the nausea analysis is based on those who chose “nausea” as the most bothersome symptom at baseline.

Disability

Disability is measured on a four-point scale: not at all (0); mild interference (1); marked interference (2); and need complete bed rest (3). 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. In addition, frequency of each category will be summarized.

Incidence of Rescue or Recurrence Medication Use

The analysis is conducted for 3 time frames, depending on rescue or recurrence medication dose time after the treatment intake: [0h<=dose<2h], [2h<=dose<24h], and [24h<=dose<=48h].

A subject is defined to have used rescue or recurrence medication if at least one medication is used during the time frame. Definitions of rescue/recurrence medication are in PROTOCOL Section 7.2.1.1.

Incidence of Headache Recurrence Through 24/48 Hours Post-Dose

It is defined that patients with pain-free at 2 hours post-dose becomes mild (1) or more before or at 24/48 hours post dose. We consider missing data as “non-recurrence” at each time point.

PGI-C

PGI-C is measured on a seven-point scale from “very much better” to “very much worse.” Responder is defined as top two categories, "very much better" and "much better". In addition, frequency of each category will be summarized.

Sustained Pain Free at 24 hours and 48 hours

Sustained Pain-Free is defined as experiencing headache pain-free at two hours after the dose and at the indicated assessment time, having not used any rescue/recurrence medications after the dose up to the assessment timing.

Time to No Disability Through 24 Hours

Disability is measured on a four-point scale: not at all (0); mild interference (1); marked interference (2); and need complete bed rest (3).

No Disability timing is defined as the first time when severity becomes 0. Note that patients with 0 severity at baseline will be excluded from the analysis.

Summary of Symptom-Free at Assessment Times (Nausea, Phonophobia, Photophobia, Vomiting)

This is 4 separate analysis of the symptom.

Total Migraine Freedom

If patients are pain free and are not experiencing any other migraine symptoms (i.e. nausea, photophobia, phonophobia, or vomiting), then they are total migraine free.

Modified Sustained Pain Free at 24 hours and 48 hours

Modified Sustained Pain-Free is defined as experiencing headache pain-free at two hours after the dose and no moderate or severe pain at the indicated assessment time, having not used any medications to treat migraine after the dose up to the assessment timing. Note that if a patient has missing evaluation at 24 hours, then he is excluded from the analysis instead of setting his response as nonresponder. The same is true at 48 hours evaluation.

Time to Meaningful Pain Relief Through 48 Hours

Meaningful Pain Relief timing is defined as the time when the corresponding eDiary question is answered as Yes.

Time to Pain Free Through 48 Hours

Pain Free timing is defined as the time when the corresponding eDiary question is answered as Yes.

Change from Baseline of EQ-5D-5L in Index Score

It is based on the EQ-5D Health Status Index Score. The Japan specific tariffs (Japanese population-based index value) for the EQ-5D Health Status Index Score is used. Change from baseline is based on Baseline (0 hour) and post-baseline (24 hours).

Change from Baseline of EQ-5D-5L in Visual Analog Scale

The change of EQ-5D-5L visual analog scale is based on Baseline (0 hour) and post-baseline (24 hours) from the onset of dosing.

HRQoL Measured by MQoLQ in 5 Domains

There are 5 domains in MQoLQ. Each domain will be analyzed separately: work functioning, social functioning, energy and vitality, feelings and concerns, and migraine symptoms. Each domain consists of 3 questions answered on a 7-point scale where 1 indicates maximum impairment and 7 indicating 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.

Treatment Satisfaction

There are 4 questions. Each question will be analyzed separately. 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)
- their willingness to take this treatment again (ranging from strongly disagree to strongly agree)
- if they would they recommend this treatment to another patient (ranging from strongly disagree to strongly agree)
- their 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").

Regarding ratio of achieving Pain Free, Pain Relief, and MBS-free, MBS-Free by Chosen Symptom up to 2 hours for each arm, corresponding figures will be created based on mITT.

5.6.4. Multiple Comparisons/Multiplicity

In order to control for overall type I error (two-sided level of significance 0.05), the gate keeping method will be used for [T1], [T2] and [T3].

5.7. Safety Analyses

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

- Adverse events
- Suicide-related thoughts and behaviors
- Vital signs and weight
- Laboratory measurements
- ECGs
- Assessment of Driving Incidents

For vital signs, weights, and labs, the baseline value is defined as the last non-missing value before or at Visit 2.

The post-baseline value is defined as the last measurement on EoS/Visit 3. Note that this study does not have any unscheduled visit and associated measurement. Therefore, there is only one post-baseline values. However, if there are multiple post-baseline values, then the last measurement on EoS/Visit 3 will be used for continuous analysis and all values after dosing will be considered as post-baseline values for categorical analysis.

5.7.1. Adverse Events

AEs will be coded by the latest Medical Dictionary for Regulatory Activities (MedDRA) version at the timing of the final DBL.

AEs are collected from Visit 1 to Visit 3.

An AE with the time of onset on or within 48 hours after a dose of study drug, or an event that worsens in intensity within 48 hours of a dose of study drug will be considered a treatment-emergent adverse event (TEAE).

Post-dose AEs are defined as the same as the TEAE except without the restriction of the 48 hours cutoff.

For each TEAE, the reported severity of the event (mild, moderate, or severe) will be determined by physicians. The Medical Dictionary for Regulatory Activities (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 (preferred term, High Level Term,

or system organ class [SOC]) is the maximum postbaseline severity observed from all associated LLTs mapping to that MedDRA level.

Serious Adverse Events (SAE) are defined in PROTOCOL Section 9.2.1.

Treatment Emergent SAE (TESAE) is an SAE which occurs within 48 hours after a dose of study drug.

Following summary will be created:

- Overview of AEs (including death, SAE, TESAE, Discontinuations from Study due to an Adverse Event, AE, post-dose AE, TEAE, TEAE related to study treatment)
- TEAEs
    - By PT by decreasing frequency
    - By PT by decreasing frequency with an incidence in any lasmiditan group ≥1.5% (common TEAE) and PT including “Vertigo”.
    - By SOC/PT (sorted alphabetically by system organ class (SOC), then by frequency in preferred term (PT))
    - By maximum severity/PT
- Post-dose AEs
    - By PT by decreasing frequency
    - By SOC/PT (sorted alphabetically by system organ class (SOC), then by frequency in preferred term (PT))
- TEAEs by PT considered to be related to investigational product by investigator
- TESAEs by PT
- TESAEs by PT considered to be related to investigational product by investigator
- SAEs by PT

Listing of AE (with TEAE flag) will be created for all randomized population

List of SAE will be created.

Note: If multiple severities are reported for a given AE and subject, then the most severe intensity will be counted. The same rule is applied for TEAEs.

Note: Patients were told not to report symptoms that usually occurred during migraine attacks (e.g. nausea).

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

5.7.2. Columbia-Suicide Severity Rating Scale (C-SSRS)

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 one month. At the following visits (Visit 2, EOS/Visit 3), the Since Last Visit version will be used to assess suicidal ideation and behavior since the last visit.

The following outcomes are C-SSRS categories and have binary responses (yes/no).

Category 1 – Wish to be Dead

Category 2 – Non-specific Active Suicidal Thoughts

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

Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

Category 5 – Active Suicidal Ideation with Specific Plan and Intent

Category 6 – Preparatory Acts or Behavior

Category 7 – Aborted Attempt

Category 8 – Interrupted Attempt

Category 9 – Actual Attempt (non-fatal)

Category 10 – Completed Suicide

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

Summary of 10 categories and "Self-injurious behavior without suicidal intent" will be created for baseline (Visit 1 and Visit 2 separately) for safety population and for all randomized population.

Summary of 10 categories and "Self-injurious behavior without suicidal intent", and 3 composite endpoints will be summarized will be created for post baseline for safety population and for all randomized population.

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

5.7.3. Vital Signs and Weights

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature.

Continuous Analysis

For vital signs of blood pressure, pulse, and temperature as well as weight and BMI, the mean change from baseline to endpoint will be summarized.

The listing will be created

Categorical Analysis

The number and percentage of patients meeting criteria for abnormalities in vital signs and weight at any time during study will be summarized by treatment. Table LAIH. 5.4 displays the criteria used to define abnormal changes in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories; the abnormal 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; 2) maximum post baseline when the direction is high.

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

Table LAIH. 5.4 Criteria for Abnormal Categorical Changes in Vital Signs

Parameter	Direction	Criteria	Patients Population defined by Baseline Categories
Systolic BP (mm Hg) (sitting)	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 (mm Hg) (sitting)	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) (sitting)	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
Temperature (° C)	Low	<35.6° C and decrease ≥1.1° C	All patients; ≥35.6° C
	High	≥38.3° C and increase ≥1.1° C	All patients; <38.3° C

Abbreviations: BP = blood pressure; bpm = beats per minute; C = degrees Celsius; kg = kilograms; mm Hg = millimeters of mercury; PCS= Potentially Clinically Significant.

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

- Systolic BP: ≤90 mmHg, ≥140 mmHg, ≥160 mmHg
- Diastolic BP: ≤50 mmHg, ≥90 mmHg, ≥100 mmHg
- Pulse: ≤60 bpm, ≥100 bpm

5.7.4. Laboratory Tests

Continuous Analysis

For continuous lab values, observed value and the mean change from baseline to endpoint will be summarized. Create both standard and conventional units' outputs.

Categorical Analysis

The incidence rates of patients with high, or low laboratory values based on Covance reference ranges at any time post-baseline will be summarized.

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

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

For analytes simply classified as normal or abnormal, patients will be defined as having an abnormal value if they have 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 abnormal laboratory values.

The incidence of patients with the following elevations in hepatic laboratory tests at any time post-baseline will also be summarized:

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

Hy's law is defined as the combination of elevation of ALT≥3× ULN and TBIL≥2× ULN, in the absence of significant cholestasis (ALP < 2 × ULN).

The analysis of elevation in ALT, AST, ALP, and TBIL will contain three subsets:

- Patients whose non-missing maximum baseline value is less than or equal to 1 × ULN for ALT, AST, ALP, and TBIL.
- Patients whose non-missing maximum baseline value is greater than 1 x ULN for ALT, AST, ALP, and TBIL, and at the same time less than or equal to 2 × ULN for ALT and AST, 1.5 x ULN for ALP and TBIL.
- Patients whose non-missing maximum baseline value is greater than 2 × ULN for ALT and AST, 1.5 x ULN for ALP and TBIL.

Note that patients with no corresponding postbaseline values will be excluded.

A listing of Subjects with abnormal Laboratory Results will be created.

A listing of Subjects with abnormal Hepatic Laboratory Results will be created.

5.7.5. ECGs

The information of ECG is captured in adverse events interpreted by investigators.

5.7.6. Assessment of Driving Incidents

Assessment of accidents/violations will be listed by patient (all randomized population). Summary table will be created (baseline and postbaseline)

5.7.7. Safety Topics of Interest

5.7.7.1. Cardiovascular Safety

Identification of Baseline Cardiovascular Disease: Identification of the subgroup of patients with baseline CVD was performed using medical history, reported by the patient at study entry. A patient was identified as having baseline CVD ("yes") if the patient had 1 or more conditions that were part of the patients' medical history or preexisting conditions in the following SMQs:Narrow terms in Cardiac arrhythmias (includes sub-SMQs; SMQ 20000049)

- Narrow terms in Cardiac failure (SMQ 20000004)
- Narrow terms in Cardiomyopathy (SMQ 20000150)
- Narrow terms in Central nervous system vascular disorders (includes sub-SMQs) (SMQ 20000060)
- Narrow terms in Embolic and thrombotic events (includes sub-SMQs) (SMQ 20000081)
- Narrow terms in Hypertension (SMQ 20000147)
- Narrow terms in Ischaemic heart disease (includes sub-SMQs) (SMQ 20000043)
- Pulmonary hypertension (SMQ 20000130)
- Torsade de pointes/QT prolongation (SMQ 20000001)

Identification of Patients with Cardiovascular Risk Factors:

CVRF is defined in Section 5.8.

Patients are summarized by the incremental presence of the above risk factors in two ways;

[1] 0 or 1 versus >=2 (2 groups summary)

[2] 0, 1, 2, 3, 4, …

Working Definitions

Definitions that were used to identify all CV AEs :

- *Potential CV AEs*: all PTs (for TEAEs and AEs) in the SMQs listed below plus PTs of abdominal pain, abdominal pain upper, and abdominal pain lower.

- *Likely CV AEs:* a subset of the potential CV AEs based on medical review and medical judgment

Potential Cardiovascular Adverse Events for the entire migraine population enrolled in the study were identified using the SMQs listed below (specifically broad and narrow terms) and then a listing of patients having an AE potentially CV in nature was generated. SMQ "narrow" terms included PTs that are highly likely to represent the condition of interest, while "broad" terms included additional PTs that may represent the condition of interest but may also prove to be of little or no interest upon closer inspection.

Broad and narrow terms in the following SMQs were used to analyze CV AEs:

- Cardiac arrhythmias (includes sub-SMQs; SMQ 20000049)
- Cardiac failure (SMQ 20000004)
- Cardiomyopathy (SMQ 20000150)
- Central nervous system vascular disorders (includes sub-SMQs; SMQ 20000060)
- Embolic and thrombotic events (includes sub-SMQs; SMQ 20000081)
- Hypertension (SMQ 20000147)
- Ischaemic heart disease (includes sub-SMQs; SMQ 20000043)
- Pulmonary hypertension (SMQ 20000130)
- Torsade de pointes/QT prolongation (SMQ 20000001)

The list of events and individual patient data were then medically reviewed to determine if the terms identified represented likely CV AE. For example, if an AE term "edema" was identified using the "Cardiac failure" SMQ broad list in a patient who experienced this AE after taking the study drug, and at the same time also reported dyspnea, had a medical history of hypertension, was taking concomitant ace-inhibitor + hydrochlorothiazide, or recently started a separate diuretic, then based on this information the AE of "edema" would represent a likely CV AE.

The listing of all potential CV AEs with reason(s) for whether or not the events were considered likely CV is provided for all randomized population. Events that are "treatment emergent" are flagged.

Following summary will be created:

- Summary and Analysis of Potential CVAE within SMQ
- Summary and Analysis of Likely CVAE within SMQ, PT
- Summary and Analysis of Likely CVTEAE within SMQ, PT
- Summary and Analysis of Potential CVAE by CVRFs by SMQ
- Summary and Analysis of Likely CVAE by CVRFs by PT
- Summary and Analysis of Likely CVTEAE by CVRFs by PT

- Patient Listing for Likely CV AEs in Patients with Categorical Changes of Interest in Vital Signs (Pulse, SBP, DBP)

- Summary and Analysis of Likely Cardiovascular Adverse Events in Patients with Categorical Changes of Interest in Blood Pressures and Pulse.

  Note: In this analysis, patients with a categorical change of interest in BP or pulse (defined in Table LAIH. 5.4) are used as the denominator whereas the numerator represents the number of patients reporting a likely CV AE. The summary is based on

  - SMQ
  - Patients with at least one Narrow scope PT in the SMQ
  - Patients with at least one Narrow or Broad scope PT in the SMQ

Concomitant Cardiovascular Medications

Cardiovascular medications were identified using the World Health Organization's ATC/Defined Daily Dose codes from a listing of all concomitant medications. These were summarized based on ATC2 codes within the "Cardiac System," as well as medications within the ATC2 code of "Antithrombotic agents" in the categories as described in Table LAIH. 5.5.

Table LAIH. 5.5 Identified Cardiovascular Medications Anatomical Therapeutic Chemical (ATC)/Defined Daily Dose

C01, Cardiac Therapy	C07, Beta-Blocking Agents
C02, Antihypertensives	C08, Calcium Channel Blockers
C03, Diuretics	C09, Agents Acting On The Renin–Angiotensin System
C04, Peripheral Vasodilators	C10, Lipid-Modifying Agents
C05, Vasoprotectives	B01, Antithrombotics

The selected medications were then reviewed by Lilly Medical to confirm that the indication for use was a CV condition (per medical history or AE). For example, any medications whose indication for use was "primary study condition" were removed because many of the CV medications are also used for migraine treatment (for example, beta blockers and calcium channel blockers).

5.7.7.2. Hepatic Safety

The percentages of patients with potentially drug-related hepatic disorders were summarized by treatment using the MedDRA PTs contained in any of the following SMQs, separately for AEs and TEAEs. Cases were then subsequently medically reviewed:

- Broad and narrow terms in the Liver-related investigations, signs, and symptoms (SMQ 20000008)
- Broad and narrow terms in the Cholestasis and jaundice of hepatic origin (SMQ 20000009)
- Broad and narrow terms in the Hepatitis, noninfectious (SMQ 20000010)

- Broad and narrow terms in the Hepatic failure, fibrosis, and cirrhosis and other liver damage (SMQ 20000013)
- Narrow terms in the Liver-related coagulation and bleeding disturbances (SMQ 20000015)

Hepatic events (AEs which can be beyond 48 hours) in the above SMQs will be summarized for safety population.

Treatment-emergent hepatic events in the above SMQs will be summarized for safety population.

Hepatic events (AEs which can be beyond 48 hours) listing with TEAE flag will be created for safety population.

5.7.7.3. Injuries and Accidents Secondary to Neurologic Adverse Events

In order to accurately capture reported injuries and accidents, all AEs in the Injury, Poisoning, and Procedural Complications SOC were reviewed. These AEs were not limited to a treatment-emergent time period (that is, 48 hours postdose). Each AE of injury, poisoning, and procedural complication was medically reviewed in order to determine if a neurologic TEAE (from the Nervous system disorders SOC) either preceded or occurred concurrently with the AE.

Following TFL will be created.

- Listing of Neurologic TEAE (already medical reviewed),

  where "Neurologic TEAE timing <= injury timing"

- Listing of Neurologic TEAE (NOT medical reviewed),

  where "Neurologic TEAE timing <= injury timing"

- Summary of "Neurologic TEAEs" and "AEs SOC=Injury, Poisoning, and Procedural Complications"
- Summary of all PTs related to the Injury, Poisoning, and Procedural Complications SOC

5.7.7.4. Suicidal Ideation and Behavior and Nonsuicidal Self-Injurious Behavior

A summary table of PTs within the Suicide/Self Injury SMQ (20000037) is provided for safety population. All AEs are presented (after Visit 1 through Visit 3.)

5.7.7.5. Hypersensitivity Events

Potential hypersensitivity reactions **(including anaphylaxis)** were summarized using the MedDRA PTs contained in any of the following SMQs for TEAEs (considered potential immediate hypersensitivity reactions) and AEs (considered potential non-immediate hypersensitivity reactions).

- Anaphylactic reaction SMQ (20000021; narrow, algorithm per SMQ guide, and broad)
- Hypersensitivity SMQ (20000214; narrow and broad)
- Angioedema SMQ (20000024; narrow and broad)

Following TFL will be created:

- Listing: Potential Immediate Hypersensitivity (<=48hours)
- Listing: Potential Non-Immediate Hypersensitivity (> 48hours)
- Summary: Potential Immediate Hypersensitivity (<=48hours)
- Summary: Potential Non-Immediate Hypersensitivity (> 48hours)

Note 1: Two listing above do not overlap. Two tables above do not overlap.

Note 2: All TFLs above are before medical review.

5.7.7.6. Serotonin Syndrome

Potential cases of Serotonin Syndrome (TEAE) are identified based on the following conditions;

- SMQ of Neuroleptic Malignant Syndrome (SMQ 20000044)
- PT terms of orthostatic hypotension, urinary incontinence, urinary retention, oesophageal dysmotility, gastroparesis, diarrhoea, faecal incontinence, constipation, muscle twitching, muscle stiffness, and muscle spasm.

The summary of the above TEAE will be created.

Then medical review is conducted for these TEAEs. These TEAEs are reviewed, and cases which preliminarily appeared that they might meet the Hunter or Sternbach criteria were then thoroughly evaluated for information including associated AEs, timing of AEs, severity, seriousness, concomitant medications, and medical history.

The listing will be created.

Note: The 2 validated sets of diagnostic criteria are the Hunter Serotonin Toxicity Criteria (Dunkley et al. 2003) and Sternbach Criteria (Sternbach 1991), with the former being more sensitive and specific.

5.7.7.7. Dizziness, Vertigo, and common TEAE

For patients experienced TEAE with PT including “Vertigo” term (Vertigo, Cervicogenic vertigo, Vertigo CNS origin, Vertigo positional, and Vertigo labyrinthine), summary of Vertigo findings will be created. The TFLs include [S1]-[S6] as specified below.

Note 1: If TEAE starting “hour” is missing, then starting hour is set as on the day of 0:00.

Note 2: If TEAE ending “hour” is missing, then ending hour is set as on the day of 23:59.

Note 3: If TEAE ending “day” and “hour” are missing, then ending day is set as Visit 3 day and hour is set as on the day of 23:59.

[S1] Frequency and Proportion of the TEAE

Note: The denominator= the number of the safety population.

[S2] Frequency of the severity (mild/moderate /severe)

[S3] The TEAE Onset time from dosing (Q1, Q2=median, Q3) (units=hours)

For this analysis, use two different methods to derive onset time from dosing:

[1] All TEAEs, including events with TEAE start time imputation.

[2] TEAEs which have non-missing TEAE start time.

[S4] Duration of the TEAE (Q1, Q2=median, Q3) (units=hours)

For this analysis, use two different methods to derive duration:

[1] All TEAEs, including events with TEAE start time imputation or end time imputation.

[2] TEAEs which have non-missing TEAE time (both start time and end time.)

[S5] Frequency and Proportion of "No interference with daily activity at 2 hours"

Note: The denominator= the number of patients who experienced the TEAE within the safety population.

[S6] Frequency and Proportion of "PGIC = better/much better at 2 hours"

Note : The denominator= the number of patients who experienced the TEAE within the safety population.

The same summary table [S1]-[S6] will be created for those who experienced TEAE with PT=Dizziness.

For common TEAE (an incidence in any lasmiditan group ≥1.5%), [S1], [S2], [S3], and [S4] will be created.

5.7.7.8. Common TEAE by intrinsic factor

Summary of common TEAE and PT having the word "Vertigo" (defined in Section 5.7.7.7) will be created by the following groups

- Gender: male/female
- Age: [Age<30] [30<=Age<50] [50<=Age<65] [65<=Age]
- BMI: [BMI <18.5] [18.5<=BMI<25] [25<=BMI<30] [30<=BMI]
- CVRF: [CVRF =0] [CVRF =1] [CVRF =2] [CVRF =3] [4<=CVRF]

Note: CVRF is defined in Section 5.8..

5.7.7.9. TEAE by Extrinsic Factor

Summary of TEAE (SOC/PT) will be created for each of these users:

- Heat Rate Lowering Medications
- Serotonergic Medications
- Contraceptives
- Non-steroidal anti-inflammatory Drugs
- CNS Sedating Medications
- Chinese Medicine

The definitions are medically reviewed before the DBL.

The summary of medication names for each of the above category will be created.

5.8. Subgroup Analysis

Subgroup analysis is summarized in Table LAIH. 5.6.

- For efficacy analyses based on proportion, the logistic regression used in [T1] will be applied to each subgroup separately. The model term includes treatment and baseline usage of preventive medications to reduce the frequency of migraine (Yes/No). The odds ratio (relative to placebo), its 95% confidence interval, and p-value will be calculated based on this model.
- For efficacy analyses based on proportion, additional logistic regression will be used. The model term includes treatment, baseline usage of preventive medications to reduce the frequency of migraine (Yes/No), subgroup, and treatment-by-subgroup interaction. The p-value for treatment-by-subgroup interaction will be displayed. The level of significance for interaction (2-sided test) is defined as 0.05 (See Section 5.4).
- For efficacy analyses based on continuous variables, ANOVA will be used for each subgroup separately. The model includes treatment and baseline usage of preventive medications to reduce the frequency of migraine (Yes/No). Change from baseline and p-values for treatment comparison will be calculated.
- For efficacy analyses based on continuous variables, additional ANOVA will be used for The model includes treatment, baseline usage of preventive medications to reduce the frequency of migraine (Yes/No), subgroup, and treatment-by-subgroup interaction. The p-value for treatment-by-subgroup interaction will be displayed. The level of significance for interaction (2-sided test) is defined as 0.05.

Table LAIH. 5.6 Subgroup Analysis

ID	Type	Analysis population [Note 1]	Dmg	PF/PR/ MBS/ Disa. at 2h	PGI-C at 2h/24h, Satisf. at 48 h	TEAE by PT	Other Analysis
SUB1	Triptan responder vs. insufficient responder (based on the most recent triptan experience)	mITT and patients who has triptan experience in lifetime	O		O	O	[1] PF/PR/MBS/disability time course (up to 48 hours) [2] EQ-5D-5L at 24h [3] Triptan detail summary at baseline

ID	Type	Analysis population [Note 1]	Dmg	PF/PR/ MBS/ Disa. at 2h	PGI-C at 2h/24h, Satisf. at 48 h	TEAE by PT	Other Analysis
SUB2	TEAE-Dizziness regardless of causality (with/without)	mITT	O	O	O	O	[1] Extended Demographic -- continuous -- vital (SBP, DBP, HR) at baseline -- categorical -- Severity of migraine attack (at 0 hour) (Mild/Moderate/Severe) At least 1 CVRF (Yes/No) Valproic acid use (on Visit 2) (Yes/No) Lomerizine use (on Visit 2) (Yes/No) Amitriptyline use (on Visit 2) (Yes/No)
SUB3	Menstrual related (yes/no)	mITT	O			O	PF/PR/MBS/disability time course (up to 48 hours)
SUB4	Body weight	mITT	O	O	O	O	
SUB5	Baseline migraine disability (need complete bed rest vs others)	mITT		O			
SUB6	Baseline headache (severe vs moderate)	mITT		O			
SUB7	Aggressive headache	mITT		O			
SUB8	Time to dose	mITT		O		O	
SUB9	Time dosed (4am-8am vs other time)	mITT		O			
SUB10	Tension type headache (Yes/No)	mITT	O	O		O	
SUB11	Mood and Anxiety disorders (Yes/No)	mITT	O	O		O	
SUB12	CVRF(CVRF<=1 vs 2<=CVRF)	mITT	O	O		O	

ID	Type	Analysis population [Note 1]	Dmg	PF/PR/ MBS/ Disa. at 2h	PGI-C at 2h/24h, Satisf. at 48 h	TEAE by PT	Other Analysis
SUB13	Patients who use migraine prevention therapy during the study.	mITT	O	O		O	
SUB14	Migraine with aura (Medical History) (with/without)	mITT	O	O			
SUB15	Gender	mITT	O	O		O	
SUB16	Age	mITT	O	O		O	
SUB17	Rescue or Recurrence Medication Use	NA				O	
SUB18	Triptan users within 3 months of informed consent (yes/no)	mITT	O		O	O	[1] PF/PR/MBS/disability time course (up to 48 hours) [2] EQ-5D-5L at 24h
SUB19	TEAE-Somnolence regardless of causality (with/without)	mITT	O	O	O		
SUB20	Triptan naïve vs. experienced (ever)	mITT	O		O	O	[1] PF/PR/MBS/disability time course (up to 48 hours) [2] EQ-5D-5L at 24h [3] Triptan detail summary at baseline
SUB21	Pain Freedom over Time	mITT					[1] Percent of patients with no disability by pain freedom (yes versus no) over time

Abbreviation of the column headers:

Dmg= Demographics; PF/PR/MBS/Disa. at 2h= Pain free, Pain Relief, MBS-Free, and Disability at 2 hours analysis (based on analysis in Table LAIH. 5.3); PGI-C at 2h/24h, Satisf. at 48 h= PGI-C analysis at 2 hours and 24 hours, and Treatment Satisfaction at 48 hours (based on analysis in Table LAIH. 5.3).

Abbreviations: CVRF = Cardiovascular Risk Factor; DBP = Diastolic blood pressure; EQ-5D-5L = EuroQol 5-dimension 5-level scale; h= hour; HR = Heart rate; ITT = intent-to-treat population;

MBS = the most bothersome symptom; mITT = modified intent-to-treat population; NA = not applicable; PGI-C = Patient Global Impression of Change; SBP = Systolic blood pressure; TEAE = Treatment emergent adverse event.

Note 1: Safety analysis (TEAE by PT) will be based on safety population. For SUB1, it is based on safety population and patients who has triptan experience in lifetime.

Definitions for each subgroup are as follows:

SUB1: Triptan responder vs. insufficient responder (based on the most recent triptan experience)

Group 1: Triptan responder: patients having experience of triptan but not in the group 2

Group 2: Triptan insufficient responder: patients who satisfy one of the conditions below d.i-d.vi

In this subgroup analysis, detailed summary of triptan usage at baseline will be created. The descriptive statistics of the response to triptans, the discontinuation reasons, and following summaries are created:

a. Summarize n (%) with triptan experience (by Visit 1)

b. Summarize number of current/prior triptans per patient, mean (range) (by Visit 1)

c Summarize number patients who used triptans within 3 months

d. Summarize triptan insufficient responders in using each method: (by Visit 1)

i. Overall response none/poor (based on most recent triptan, either ongoing [start date <= V1 and ongoing or if no ongoing triptan, most recent]) (most recently used triptans)

ii. Inconsistent response (based on most recent triptan, either ongoing [start date <= V1 and ongoing or if no ongoing triptan, most recent])

iii. Triptan discontinuer

Note: Reason for discontinuation is captured in CRF. The triptan discontinuer is defined for those patients who choose one of the followings:

"Lack of pain freedom at 2 hours",

"Lack of pain relief at 2 hours",

"Did not return function or eliminate disability",

"Inconsistent response",

"Migraine recurrence",

"Intolerance to Medication",

"Did not relieve associated symptoms",

"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".

iv. mTOQ poor response (based only on ongoing most recent triptan – Current Triptan users Patients who have a score of poor or very poor using the mTOQ). The definition is based on [mTOQ-6 Conversion Method 2] in Section 5.5.3.

v. Composite triptan insufficient responder (satisfying at least one of [ii], [iii], or [iv])

vi. Triptan Contraindicated patients. Defined as patients who have at least one of the following SMQ terms (Narrow Scope PT):

- 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
- Ischaemic stroke
- Transient ischaemic attack
- Peripheral vascular disorder
- Raynaud's phenomenon
- Superior mesenteric artery syndrome
- Labile hypertension
- Prinzmetal angina
- Cerebrovascular disorder
- Malignant hypertensive heart

SUB2: TEAE-Dizziness regardless of causality (with/without)

Group 1: Patients with TEAE Dizziness regardless of causality

Group 2: Otherwise.

SUB3: Menstrual related (yes/no)

Group 1: Female with menstruation at least one day in [Day(-2), Day(-1), Day 1, Day 2, Day 3] of dosing.

Group 2: Otherwise.

Note: Day 1 is the day when a patient takes the treatment. Day(-1) is one day before Day 1.

SUB4: Body weight

Group 1: weight <=median
Group 2: median < weight

SUB5: Baseline migraine disability (need complete bed rest vs others)

Group 1: Patients who has Baseline (0 hour) migraine disability (need complete bed rest)

Group 2: Otherwise.

SUB6: Baseline headache (severe vs moderate)

Group 1: Patients who has Baseline (0 hour) headache severity= severe.

Group 2: Otherwise.

SUB7: Aggressive headache

Group 1: Patients who satisfy both [Condition 1] and [Condition 2]:

[Condition 1] Dosing time – Migraine onset <=1hour

[Condition 2] Baseline severity=severe

Group 2: Otherwise.

SUB8: Time to dose

Based on dosing time and onset of migraine, 2 groups are defined as follows:

Group 1: dosing time <1 hour
Group 2: 1 hour <= dosing time

SUB9: Time dosed (4am-8am vs other time)

Group 1: Patients who has dosing in the morning, [4am<=dosing <=8am]

Group 2: Otherwise.

SUB10: Tension type headache (Yes/No)

Group 1: Patients who has PT= [Tension headache] as comorbid condition

Group 2: Otherwise.

SUB11: Mood and Anxiety disorders (Yes/No)

Group 1: Patients who has following PT as medical history,

Agitated depression, Childhood depression, Depression, Depression suicidal, Menopausal depression, Major depression, Perinatal depression, Persistent depressive disorder, Depressed mood, Depressive symptom, Mixed anxiety and depressive disorder, Anxiety disorder, Social anxiety disorder, Anxiety, Generalized anxiety disorder, Bipolar disorder, Bipolar I disorder, Bipolar II disorder

Group 2: Otherwise.

SUB12: CVRF(CVRF<=1 vs 2<=CVRF)

Group 1: Patients with CVRF <=1

Group 2: Patients with CVRF >=2

Note: The CVRF is defined as follows. (Reference: Comprehensive risk management chart for cerebro-cardiovascular disease 2019; The Japan Society of Internal Medicine (Vol.104-4))

CVRF1: Current smoker at baseline (Visit 1)

CVRF2: Hypertension, patients having condition at baseline (Visit 1) below a) or b)

a) Narrow terms in Hypertension (SMQ 20000147)
b) Baseline blood pressure is systolic >=140mmHg, or diastolic >=90mmHg

CVRF3: Diabetes at baseline (Visit 1) (including impaired glucose tolerance, patients having condition below a) or b)

a) Comorbidity PT: Diabetes mellitus, Type 1 diabetes mellitus, Type 2 diabetes mellitus, Latent autoimmune diabetes in adults, Hyperglyceridaemia, Cataract diabetic, Diabetic nephropathy, Diabetic autonomic neuropathy, Diabetic retinopathy, Impaired glucose tolerance

b) Baseline blood sugar level, non-fasting Glucose >=200 mg/dl

CVRF4: Dyslipidemia, patients having condition at baseline (Visit 1) below:

Comorbidity PT: Hypercholesterolaemia, Hyperlipidaemia, Dyslipidaemia, Type IIa hyperlipidaemia, High density lipoprotein decreased, Low density lipoprotein increased, Metabolic syndrome, Hypertriglyceridaemia.

CVRF5: Chronic kidney disease (only Comorbidity PT term) at baseline (Visit 1)

CVRF6: Obesity (BMI >=25) at baseline (Visit 1)

CVRF7: Age at baseline (Visit 1)

Male patients: age >=45 years old,

Female patients: age >=55 years old,

CVRF8: Gender, patients below a) or b)

a) Male
b) Postmenopausal female (defined in Table LAIH. 5.7)

Table LAIH. 5.7 Definition of Postmenopausal female

Baseline FSH	Menstrual Period Question in CRF (YES/NO)	Postmenopausal?
FSH >40mIU/mL	NO	YES
FSH >40mIU/mL	YES	YES
FSH <=40mIU/mL or missing	NO	YES
FSH <=40mIU/mL or missing	YES	NO

Abbreviation: CRF = case report form FSH = follicle-stimulating hormone.

CVRF9: Family (Parents, Grandparents, and siblings) history of CVD (Yes for Coronary artery disease, Cardiovascular disorder, or Cerebrovascular disorder in eCRF "Associate Person Medical History: Special Interest")

SUB13: Patients who use migraine prevention therapy during the study.

Note: This is based on CRF, not IWRS.

Group 1: Patients who use migraine prevention therapy

Group 2: Otherwise.

SUB14: Migraine with aura (Medical History) (with/without)

Group 1: Patients having migraine with aura in medical history.

Group 2: Otherwise

SUB15: Gender

Group 1: Male

Group 2: Female

SUB16: Age

Group 1: Age <=median
Group 2: median < Age

SUB17: Rescue or Recurrence Medication Use

Patients who use rescue or recurrent medication at specific time (0 hour is dosing time) defined below.

Group 1: 0 hour <= medication use <=2 hour

Group 2: 2 hours < medication use <=24 hour

Group 3: 24 hours < medication use <=48 hours

Note: Patients can be in multiple groups.

SUB18: Triptan users 3 months prior to informed consent (yes/no)

Group 1: Patients who used at least one triptan within 3 months of informed consent.

Group 2: Otherwise

SUB19: TEAE-Somnolence regardless of causality (with/without)

Group 1: Patients who has at least one TEAE-Somnolence regardless of causality

Group 2: Otherwise.

SUB20: Triptan naïve vs. experienced (ever)

Group 1: Triptan experienced = patients who has triptan experience in lifetime

Group 2: Otherwise.

SUB21: Pain Freedom over Time

At each postbaseline time point, subgroup is defined as

Group 1: Patients who achieved pain freedom at the time point.

Group 2: Otherwise.

Percent of patients with no disability by pain freedom (yes versus no) over time will be displayed. There is no statistical test. Missing data were excluded from the analysis at each time point. For patients who took rescue medication, data were also excluded.

5.9. CCI

For more details of [T1], [T2], and [T3], see Section 5.6.1.

5.10. Unblinding Plan

During the study, some members are unblinded (Table LAIH. 5.8). These members will not be allowed to join meetings which may affect the other members' blind condition, such as trial level safety review (TLSR) and data review meetings.

Table LAIH. 5.8 Unblinded Members through LAIH Study

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	To manage and track sample shipping	CLRM

Abbreviations: CLRM = Clinical Laboratory Results Modernization; e-CTS = Enhanced Clinical Trials System; EU = European Union; SAE = Serious Adverse Event.

5.11. 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 which will be converted to an XML file. Both SAEs and 'Other' AEs are summarized: by treatment group, by MedDRA PT (preferred term).

- An AE is considered 'Serious' whether or not it is a TEAE (Definitions of AE and TEAE are in Section 5.7.1).
- 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:
  - the number of participants at risk of an event
  - the number of participants who experienced each event term
  - the number of events experienced.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

5.12. Interim Analysis

There is no interim analysis.

6. References

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7. Appendices

Appendix 1. eDiary Assessments

	Visit 2	Predose	Postdose							
eDiary Assessment for attacks treated with study drug		**0h**	**0.5h**	**1h**	**1.5h**	**2h**	**3h**	**4h**	**24h**	**48 h**
Headache severity (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain)		X	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	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							X	
Disability		X	X	X		X			X	
PGI-C						X			X	
Treatment Satisfaction										X

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

PPD