Statistical Analysis Plan: I5Q-JE-CGAN(a) A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients with Episodic Migraine

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1. Statistical Analysis Plan for Protocol: I5Q-JE-CGAN: A Randomized, Double-Blind, Placebo-Controlled Study of LY2951742 (Galcanezumab) in Japanese Patients with Episodic Migraine

LY2951742 (Galcanezumab)

I5Q-JE-CGAN is a multisite, randomized, double-blind, placebo-controlled, bridging study of galcanezumab in Japanese outpatients suffering from episodic migraine. The study is comprised of 4 periods: 1) Screening (3-45 days), 2) Baseline for assessment of the type, frequency and severity of headaches (30-40 days), 3) Double-blind treatment phase (6 months), and 4) Follow-up (4 months). Patients who complete Study Period III may have an option to roll-over to the open-label extension study, I5Q-JE-CGAP. Patients will be randomized 2:1:1 to either placebo, 120 mg, or 240 mg LY2951742 administered as a subcutaneous (SC) injection once every month.

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I5Q-JE-CGAN

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

Approval Date: 15-Nov-2018 GMT

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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 first unblinding.

Following topics are major updates from I5Q-JE-CGAN (CGAN) protocol. Corresponding SAP sections are also specified:

- PROTOCOL Section 4. Several analysis definitions were modified to align with I5Q-MC-CGAG (CGAG) study and I5Q-MC-CGAI (CGAI) (SAP Table CGAN. 4.1, Table CGAN. 4.2, and Table CGAN. 4.3):
  - Key secondary: The definition of "The overall mean change from baseline in the number of monthly **migraine headache days or headache days** requiring medication for the acute treatment of **migraine headache or headache** during the 6-month, double-blind treatment phase" was modified. It was intended to be the same analysis as "The overall mean change from baseline in the number of monthly **migraine headache days** requiring medication for the acute treatment of **migraine** during the 6-month double-blind treatment phase" in other secondary objective. Eventually the other secondary objective was deleted.
  - Other secondary: HCRU analysis method was changed from statistical models to simple descriptive statistics.
  - Exploratory: MSQ categorical analysis (Role Functional Preventive) was omitted.
  - Exploratory: MSQ categorical analysis (Emotional Functional domain) was omitted.
  - Exploratory: MSQ categorical analysis (Role Functional restrictive) definition was modified.
  - Exploratory: "allergic reactions or hypersensitivity" was deleted.
  - Exploratory: "To compare galcanezumab with placebo with respect to the proportion of migraine headache days or headache days requiring medication for the acute treatment of migraine headache or headache" was deleted.
- PROTOCOL Section 10.2. Safety Population and ADA follow-up Cohort were added to align with CGAG. Safety Population would be used for safety analysis and exposure, instead of ITT population to align with CGAG (SAP Section 5.5.1.3).
- PROTOCOL Section10.3.1. Regarding multiplicity adjustment, the protocol stated, "For the primary analysis and the other continuous efficacy analyses, multiplicity adjustment (120 mg versus placebo and 240 mg versus placebo), such as Dunnett's procedure, will be used if appropriate." The SAP stated that the multiplicity test would be performed only for the primary analysis with step-down Dunnett's procedure to control overall type one error in this study. Originally ANCOVA with LOCF was planned for various efficacy and health outcome measures. CGAG deleted them. Hence these were deleted except for the primary efficacy analysis in CGAN (SAP Table CGAN. 5.5).
- PROTOCOL Section 10.3.2.3. Originally abortive medication related analysis were based on information collected through ePRO only. Additional information captured

through eCRF will be utilized in order to have more accurate analysis (SAP Section 5.5.8, Section 5.5.9).

- PROTOCOL Section 10.3.2.4. Originally treatment compliance was out of scope for summary. It was add to align with CGAG (SAP Section 5.5.6).
- PROTOCOL Section 10.3.3.3. SP III and SP IV combined analysis were omitted for other secondary and exploratory efficacy. Because many patients would skip SP IV and rollover to CGAP study, efficacy analysis would be less informative (SAP Table CGAN. 5.5).
- PROTOCOL Section 10.3.4. SP III and SP IV combined analysis was added for TEAE ADA to align with CGAG (SAP Section 5.5.12.1.6). There was no safety related time-to-event analyses using SP III and SP IV combined. Hence this statement is not applicable in SAP Version 2.
- PROTOCOL Section 10.3.4.4. Categorical analysis (LOCF) for TE vital and TE weight were omitted (SAP Section 5.5.12.2). "Any time postbaseline" analysis would be sufficient.
- PROTOCOL Section 10.3.4.6. Categorical analysis (LOCF) for TE laboratory were omitted (SAP Section 5.5.12.2). "Any time postbaseline" analysis would be sufficient.
- PROTOCOL Section 10.3.6.1 MIDAS analysis (each item score) for SP III and SP IV combined were omitted (SAP Section 5.5.11.2) because many patients would skip SP IV and rollover to CGAP study.

Including the above modifications/update/deletion from the PROTOCOL, followings are major changes (e.g. change of definition, a new analysis specifically for this study) from SAP Version 1 to SAP Version 2. Minor updates (e.g. clarification of definitions, and adding listings, adding examples for clarification) were not listed in general.

- Table CGAN. 4.1: "To compare LY2951742 with placebo with respect to change in use of acute (abortive) migraine treatment" was as updated to "To compare LY2951742 with placebo with respect to change in use of acute (abortive) migraine treatment (MHD only)".
- Table CGAN. 4.3: "To compare LY2951742 with placebo with respect to the proportion of migraine headache days or headache days requiring medication for the acute treatment of migraine headache or headache" was deleted. It was intended to be the same analysis as "To compare LY2951742 with placebo with respect to the proportion of migraine headache days requiring medication for the acute treatment of migraine headache".
- Table CGAN. 4.3: In the analysis "To compare LY2951742 with placebo with respect to categorical changes in quality of life," MSQ categorical analysis was modified. More specifically, cutoff value of the sub score MSQ Role Function-Restrictive domain was changed from 10.9 to 25. The other 2 sub scores' response analysis were omitted. Analysis of "allergic reactions or hypersensitivity in SP IV" was omitted.
- Section 5.4.1:
  - "Number of migraine headache days with menstrual period" was added.

  - "Number of weekly migraine headache days in Month 1" was added.
  - "Number of days with abortive medication use on non-headache days".
- Section 5.4.2.1.1: PGI-S responder analysis was added.
- Section 5.4.2.1.2: PGI-I responder analysis (Weighted Mean of PGI-I Responder analysis) was added.
- Section 5.4.3.4: PSMQ-M positive response definition was added.
- Section 5.5.1: Following updates were made:
  - Regarding multiplicity adjustment, the protocol stated, "For the primary analysis and the other continuous efficacy analyses, multiplicity adjustment (120 mg versus placebo and 240 mg versus placebo), such as Dunnett's procedure, will be used if appropriate." The SAP stated to be performed only for the primary analysis with Step-down Dunnett's procedure.
  - LY_All arm (LY120 and LY240 combined) was defined. Also, general sorting rules were specified with LY_All and total.
  - Derivation of efficacy analysis baseline related values was clarified (based on eligibility day derived from ePRO data, not IWRS).
- Section 5.5.1.3: "All Patients", "ADA follow-up cohort", "Safety Population" were added.
- Section 5.5.1.4, Table CGAN. 5.4 was modified:
  - Continuous safety analyses for SP IV and C-SSRS for SP IV were added.
  - Analysis population for safety related analysis for SP III were updated as safety population from ITT population.
  - Immunogenicity analysis SP IV was deleted. Population for SP III and SP IV combined analysis were updated, including ADA follow-up cohort.
  - Some baseline definitions were updated to align with the other baseline definitions.
- Section 5.5.3: Important protocol deviation categories were updated. Complete definitions and detective methods were specified in a separate document.
- Section 5.5.4: Baseline definitions (with corresponding visits) were clarified for each variables.
- Section 5.5.4: New variables were added:
  - Age [<20, >=20]
  - Years since migraine diagnosis
  - Number of comorbid conditions
  - Efficacy (used for change from baseline) and health outcome related baselines listed in Table CGAN. 5.5.
  - Baseline values used for subgroup analysis
  - Baseline MHD category by ePRO.
  - Summary of Baseline MHD difference by IWRS and ePRO eligibility day.

  - Previous migraine prevention treatment
  - Number of previous migraine prevention treatment fail (Visit 1)
  - Number of Comorbid conditions other than migraine
  - Baseline values for subgroups

- Section 5.5.4: Definition and summary methods were updated for "Medical history" and "Pre-existing conditions"
- Section 5.5.5: "In addition, injections not administered" was omitted. Two listings were added:
  - Listing of subjects with exposure to investigational product
  - Listing of treatment exposure with package number and internal lot number
- Section 5.5.6 Treatment Compliance: The formula was updated to account for early discontinuation patients.
- Section 5.5.7: Summaries of categorical compliance (>=50%, >=80%) were added.
- Section 5.5.8: The definitions of "previous migraine prevention therapy", "migraine prevention therapy", "previous migraine acute treatment" and "migraine acute treatment" were updated to capture as much medication as possible. Categories of "Acute Migraine treatment" were specified.
- Section 5.5.10.1: Method Of Moment (MOM) was deleted. Based on recent global study results, there were no convergence issues for MMRM.
- Section 5.5.10.1: Effect size summary based on the primary analysis was added.
- Section 5.5.10.1: Implementation method for step-down Dunnett was specified. PROC GLIMMIX would be used instead of PROC MIXED because PROC MIXED did not have the option.
- Section 5.5.10.2: Sensitivity analysis by IWRS eligibility day was added.
- Section 5.5.10.3: Table CGAN. 5.5 was updated with new analysis defined in other sections. The following general rule was added: If analysis results would be considered less informative, (e.g. change from baseline analysis with rare baseline events,) then such results may not be provided in CSR.
- Section 5.5.11.3: HCRU analysis was simplified.
- Section 5.5.11.4: PSMQ-M analysis was simplified.
- Section 5.5.12.1: FEAE baseline definition was updated to align with the other baseline definitions in this study.
- Section 5.5.12.1.1.1 Hypersensitivity events: The section name was changed from "Allergic/hypersensitivity events" to "Hypersensitivity events". Definition of SMQ was updated. The hypersensitivity analysis in SP IV was omitted.
- Section 5.5.12.1.1.2: The section name was changed from "injection site reactions" to "adverse events related to injection sites". Timing of injection AEs were updated to align with CGAN CRF (different from hypersensitivity events timing recorded in CGAN CRF). "Summary of Injection Site Reaction by Max Severity, by Anatomical Location" was added for a medical request. "Figure of duration of Injection Site related Adverse Events" was added.
- Section 5.5.12.1.3 Table CGAN. 5.6: For Temperature, unit and criteria were updated to fit Japan use. A shit table was deleted. To align with the other vital analysis, analysis patients population were updated for
  - Systolic BP, PCS High
  - Diastolic BP, PCS High

  - Temperature
- Section 5.5.12.1.4: For ECG and heart rate, data exclusion criteria were omitted because the information was not captured in this study. In Table CGAN. 5.7, ">500msec" criteria was labeled as "PCS High" for QTcF and QTcLCTPB analysis. Definition of qualitative ECG baseline was added.
- Section 5.5.12.1.5: Hy's law was modified.
- Section 5.5.12.1.6: ADA follow-up cohort analysis was added. A line plot was omitted.
- Section 5.5.13: Body weight subgroup was added. MHD 50% response rate analysis was added for the treatment resistant status subgroup.
- Section 5.7 Table CGAN. 5.10. Unblinding members and reasons were updated. CTPM was added.
- Section 5.8.1: TFLs for interim analysis were updated. In particular, immunogenicity related TFLs were out of scope for the interim.

4. Study Objectives

4.1. Primary Objective

The primary efficacy objective is to test the hypothesis that at least one dose of LY2951742 (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with episodic migraine. Superiority is defined as greater improvement for LY2951742 compared with placebo as measured by the overall mean change from baseline in the number of monthly migraine headache days during the 6-month double-blind treatment phase.

A migraine headache day is defined as any calendar day with a headache lasting longer than 30 minutes that meets the criteria for migraine or probable migraine (see endpoint definition in Table CGAN. 5.1).

4.2. Secondary Objectives

4.2.1. Key Secondary Objectives

Key secondary objectives listed in Table CGAN. 4.1 reflect comparisons of each LY2951742 dose with placebo.

Table CGAN. 4.1 List of Key Secondary Objectives and Their Endpoints

Objectives	Endpoints
To compare LY2951742 with placebo with respect to 50% response rate	The proportion of patients with reduction from baseline ≥50% in monthly migraine headache days during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to 75% response rate	The proportion of patients with reduction from baseline ≥75% in monthly migraine headache days during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to 100% response rate	The proportion of patients with reduction from baseline =100% in monthly migraine headache days during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to change in functioning	Mean change from baseline in the Role Function-Restrictive domain score of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v2.1) (average of Months 4, 5, and 6)
To compare LY2951742 with placebo with respect to change in use of acute (abortive) migraine treatment	The overall mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to change in global severity of the migraine condition	Mean change from baseline in the Patient Global Impression of Severity (PGI-S) score (average of Months 4, 5, and 6)

4.2.2. Other Secondary Objectives

The secondary objectives listed below in Table CGAN. 4.2 reflect the comparison of LY2951742 (120 or 240 mg/month) with placebo.

Table CGAN. 4.2 List of Other Secondary Objectives and Their Endpoints

Other Secondary Objectives	Endpoints
To compare LY2951742 with placebo with respect to change in headache days	The overall mean change from baseline in the number of monthly headache days during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to change in moderate to severe headache days	The overall mean change from baseline in the number of monthly moderate to severe headache days during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to 30% response rate	The proportion of patients with reduction from baseline ≥30% in monthly migraine headache days during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to distribution of response rates	Cumulative distribution of monthly migraine headache day response rates (0%, 5%, 10%,…,95%, 100%) during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to time to first 50% response	Time to first occurrence (in months) of a ≥50% reduction from baseline in the number of monthly migraine headache days (Kaplan-Meier analysis)
To compare LY2951742 with placebo with respect to onset of effect	The initial month at which statistical separation in mean change from baseline in the number of monthly migraine headache days is demonstrated and maintained at all subsequent months through Month 6
To compare LY2951742 with placebo with respect to onset of 50% sustained response	The initial month at which statistical separation in the proportion of patients meeting at least a 50% reduction in monthly migraine headache days that is sustained at all subsequent months through Month 6
To compare LY2951742 with placebo with respect to maintenance of 50% response	The proportion of patients who maintain 50% response criteria for at least 3 consecutive months to the patient's endpoint during double-blind treatment phase. The proportion of patients who maintain 50% response criteria for 6 consecutive months during double-blind treatment phase
To compare LY2951742 with placebo with respect to changes in other efficacy parameters, specifically: • International Classification of Headache Disorders (ICHD) migraine headache day • migraine attacks • migraine headache hours • headache hours • severity of remaining migraines	Overall mean change from baseline (during the 6-month double-blind treatment phase) on the following monthly measures: • ICHD migraine headache days • migraine attacks • migraine headache hours • headache hours • severity of remaining migraines

Other Secondary Objectives (cont.)	Endpoints (cont.)
To compare LY2951742 with placebo with respect to global assessment of illness	Overall Patient Global Impression-Improvement (PGI-I) rating during the 6-month double-blind treatment phase
To compare LY2951742 with placebo with respect to changes in disability and quality of life	Mean change from baseline on the following measures: • the Migraine Disability Assessment test (MIDAS) total score and individual items at Months 6 • the Migraine-Specific Quality of Life Questionnaire, version 2.1 (MSQ v2.1) total score, and Role Function-Preventive and Emotional Function domain scores (average of Months 4, 5, and 6) Descriptive summary at each visit for the following measure: • the HealthCare Resource Utilization (HCRU) and employment status
To evaluate patient satisfaction with medication	Satisfaction with medication using the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M)
To compare LY2951742 with placebo with respect to safety and tolerability	Analysis of: • treatment emergent adverse events (TEAEs) • discontinuation rates • vital signs and weight • electrocardiograms (ECGs) • laboratory measures • Suicidality using the Columbia Suicide Severity Rating Scale (C-SSRS) • Other safety parameters
To evaluate immunogenicity of LY2951742	Throughout the study: • Development and consequences of anti-drug antibodies and neutralizing anti-drug antibodies to LY2951742
To evaluate pharmacokinetics of LY2951742	Serum concentrations of LY2951742
To evaluate pharmacodynamics (target engagement) of LY2951742	Plasma concentrations of CGRP
To assess changes in efficacy outcomes during Study Period IV as collected by electronic patient-reported outcomes (ePRO) diary data	In Study Period IV: • Mean changes from baseline in migraine headache days (SP III and SP IV combined) • Time to first loss of response (in SP IV) among patients who meet the 50% response rate criteria at the end of the double-blind treatment phase • Time to initiation of treatment with a migraine prevention medication (in SP IV)

Abbreviations: CGRP = calcitonin gene-related peptide; MHD = migraine headache day.

4.3. Exploratory Objectives

Some of the exploratory objectives are listed here.

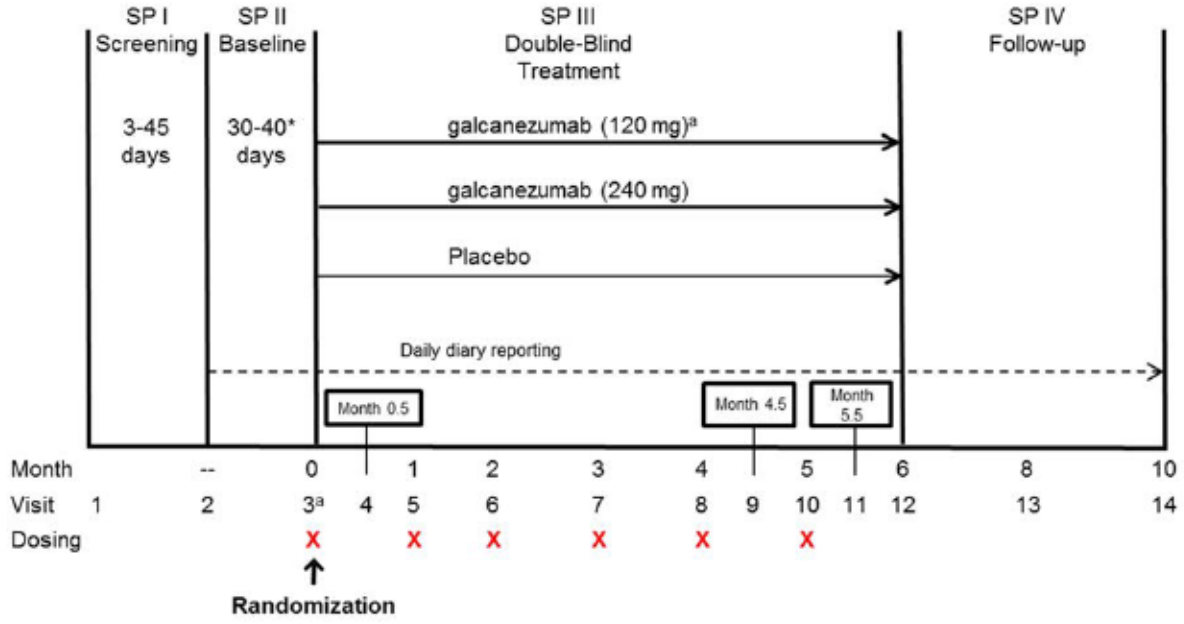
Table CGAN. 4.3 List of Some Exploratory Objectives and Their Endpoints

Objectives	Endpoints
To explore pharmacogenetics	Analysis of genetic variation on response, safety, and tolerability to LY2951742 treatment
CCI	
To compare LY2951742 with placebo with respect to categorical changes in quality of life	Percentages of patients with • ≥50% improvement in MIDAS total score at Month 6 • change from baseline in MSQ Role Function-Restrictive domain ≥25 (average of Months 4, 5, and 6)
To compare LY2951742 with placebo with respect to the proportion of migraine headache days requiring medication for the acute treatment of migraine headache	Change from baseline in the proportion of monthly migraine headache days requiring medication for the acute treatment of migraine headache
To compare LY2951742 with placebo with respect to changes in symptomatology associated with migraine or probable migraine	Change from baseline in the number of monthly migraine headache days with • nausea and/or vomiting • photophobia and phonophobia • aura • prodromal symptoms other than aura
To explore safety results during Study Period IV	Analysis of the following during Study Period IV: • FEAEs • discontinuation rates • vital signs and weight • ECGs • laboratory measures • other safety parameters, including suicidality using the C-SSRS.

Abbreviations: CGRP = calcitonin gene-related peptide; C-SSRS = Columbia–Suicide Severity Rating Scale; FEAE = follow-up-emergent adverse event; ECG(s) = electrocardiogram(s); MIDAS = Migraine Disability Assessment test; MSQ = Migraine-Specific Quality of Life Questionnaire version 2.1; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

5. A Priori Statistical Methods

5.1. Study Design



*Eligibility period determined between a minimum of 30 days and a maximum of 40 days. Investigators may have up to 5 additional days (beyond the 40 days) if needed to schedule patients' Visit 3 appointment.

[a]Patients randomized to the 120 mg dose will receive a loading dose of 240 mg at the first injection only (Visit 3).

Approximately 240 enrolled patients roll-over to I5Q-JE-CGAP study (Open Label Extension) at visit 12

Abbreviations: SP = study period.

Figure CGAN.5.1. Study I5Q-JE-CGAN protocol design.

5.2. Determination of Sample Size

The study will enroll approximately 451 patients. Eligible patients will be randomized in blinded fashion in a 2:1:1 ratio to placebo (target of 225 patients), galcanezumab 120 mg/month (target of 113 patients), or 240 mg/month (target of 113 patients). With the assumption of a 15% discontinuation rate and an effect size of 0.36, it is estimated that this sample size will provide approximately 88% power that at least 1 dose of galcanezumab will separate from placebo at a two-sided significance level of 0.05 based on simulations using the Dunnett' s test (Dunnett 1955). Assumptions in the simulations were based on the assumptions for global Phase 3 studies, with adjustment to reflect less dropout and less variability in a more homogenous Japanese study.

Approximately 902 patients may be screened to ensure randomization of 451 patients, with an estimated 383 patients completing the study.

5.3. Randomization and Treatment Assignment

Patients will be randomized in a blinded fashion to LY2951742 120 mg, 240 mg, or placebo with a randomization ratio of 2:1:1 (about 225 on placebo, 113 on LY2951742 120 mg, and 113 on LY2951742 240 mg). To achieve between-group comparability, the randomization will be stratified by baseline migraine frequency (<8 migraine headache days versus ≥8 migraine headache days). To ensure an appropriate balance of low- and high-frequency migraine headache-day patients, the sponsor will stop enrollment of low-frequency patients, if the number exceeds an estimated 315.

5.4. Endpoints

5.4.1. Efficacy Endpoints

Migraine and headache endpoints are defined in Table CGAN. 5.1. Each month is defined as a 30-day period with migraine or headache measures normalized from the visit intervals.

Table CGAN. 5.1 Migraine and Headache Endpoint Definitions

Diagnosis	Definition/Criteria
Migraine headache	A headache, with or without aura, of ≥30 minutes duration with both of the following required features (A and B): A. At least 2 of the following headache characteristics: • Unilateral location • Pulsatile quality • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity AND B. During headache at least 1 of the following: • Nausea and/or vomiting • Photophobia and phonophobia *(Definition adapted from the IHS ICHD-3 beta)*
Probable migraine headache	A headache missing 1 of the migraine features in the IHS ICHD-3 beta definition such that 1 feature in criteria A is missing or 1 feature in criteria B is missing; that is, meet at least 2 A criteria and none of the B criteria, or meet 1 of the A criteria and at least 1 of the B criteria.
Migraine headache day	A calendar day on which a **migraine headache or probable migraine headache** occurred.
Migraine headache attack	Beginning on any day a migraine headache and/or a probable migraine headache is recorded, and ends when a migraine-free day occurs.
Non-migraine headache	All headaches of at least 30 minutes duration not fulfilling the definition of migraine or probable migraine.
Non-migraine headache day	A calendar day on which a non-migraine headache occurred.
Headache day	A calendar day on which any type of headache occurs, (including migraine headache, probable migraine headache, and non-migraine headache).
Migraine headache days with abortive (acute) medication use	Calendar days on which migraine or probable migraine occurs, requiring abortive (acute) medication.
ICHD migraine headache day	A calendar day on which a migraine headache occurs.

Abbreviations: ICHD = International Classification of Headache Disorders; IHS = International Headache Society.

Headache information will be collected via an electronic patient reported outcome (ePRO) diary. Patients will need to enter diary data daily beginning from Visit 2, continuing until Visit 14.

Information recorded in the ePRO diary, the possible responses and the assignment to the type of headache is presented in Table CGAN. 5.2.

Table CGAN. 5.2 ePRO Diary Questions, Responses, and Assignment to Headache Type

QUESTION	RESPONSES	HEADACHE ASSIGNMENT
Q1. Yesterday, did you have a headache that lasted for thirty minutes or more?	Yes	Migraine if at least two migraine Criteria A's and at least one migraine Criteria B.
	No[a]	
Q2. Enter the total number of hours you had a headache yesterday.	Range 1 to 24	If ≥1, the headache will be counted as a headache day.
Q3. Yesterday, what was the worst headache pain?	Mild	
	Moderate	Migraine Criteria A
	Severe	Migraine Criteria A
Q4. Yesterday, was the headache throbbing or pounding?	Yes	Migraine Criteria A
	No	
Q5. Yesterday, was the headache just on the right or left side of your head?	Yes	Migraine Criteria A
	No	
Q6. Yesterday, was the headache made worse by your usual daily activity	Yes	Migraine Criteria A
	No	
Q7. Yesterday, did the headache come with sensitivity to light and sound?	Yes	Migraine Criteria B
	No	
Q8. Yesterday, did you feel sick to the stomach or throw-up with the headache?	Yes	Migraine Criteria B
	No	
Q9. Yesterday, did you have your menstrual period (if female)?	Yes	
	No	
Q10. Yesterday, did you take any medicine for your headache?	Yes	Medication will only count as headache medication on a day a headache occurred.
	No	
Q11. Yesterday, did you take any medication for pain other than headache?	Yes	
	No	
Q12. Yesterday, did you experience aura?	Yes	
	No	
Q13. Yesterday, did you experience any warning symptoms other than aura (prodrome symptoms) that a migraine was coming?	Yes	
	No	

[a] If "No" is answered for Q1, then the patients will skip Q2 - Q6, only answer questions Q7 - Q13.

Primary Measure: the Number of Monthly Migraine Headache Days

The primary measure is the number of monthly migraine headache days. A migraine headache day is defined as a calendar day on which a **migraine or probable migraine** occurs.

The primary measure of the number of monthly migraine headache days will be summarized from the daily ePRO data for each patient in that period (including 30 days of daily data from the baseline period prior to randomization, 6 months of daily data during the treatment phase, and 4 months of daily data during the post-treatment phase).

The daily data will be aggregated, and the number of migraine headache days will be provided for each of the 30-day periods. In calculating the number of migraine headache days for each period, if the period is not equal to 30 days, the number of migraine headache days will be normalized by multiplying the number of migraine headache days by (30/x) where 'x' is the total number of non-missing diary days in the period.

For the baseline period (Visit 2 to Visit 3), once a patient becomes eligible before Visit 3 judged from the daily ePRO data (this is called **eligible day**), then all ePRO data after the eligible day to Visit 3 will be ignored.

Example: A patient has Visit 2 = 2016/Jan/1. He records diary on Jan/2 for his headache information on Jan/1. He records diary everyday (no missing data.) He records diary on Jan/31 for his headache information on Jan/30 which ends up as 5th migraine headache day during the baseline period (starting from Jan/1.) He becomes eligible for CGAN study (assuming all other eligibility conditions are met.) He goes to a site on Feb/ 4 (Visit 3) and gets 1st injection on the day. In this case **eligible day** is 2016/Jan/30. All diary data of Jan/1, Jan/2,…, Jan/30 will be used as baseline period data. All diary data of Jan/31, Feb/1, Feb/2, Feb/3 will be ignored. Diary data on Feb/4 (Visit 3) is used for Month 1 period data.

For the double blind period (SP III), Month 1 period data is based on headache information from Visit 3 up to on Visit 5 – 1 day. Month 2 period data is based on headache information from Visit 5 up to Visit 6 – 1 day. Month 3, to Month 6 will be defined similarly.

For the 4 months of the post-treatment period, the monthly interval will be derived as below. Firstly, the 2-month visit interval will be split into two one-month periods for efficacy measures. If the number of days between two visits (visit x + 1 date - visit x date + 1) is even, the first half will be in the first one-month period and the second half will be in the second one-month period. If the number of days between two visits is odd, then the days will be split similarly, but the first one-month period will have one day more than the second one-month period. Secondly, after the two-month visit intervals are split into two one-month periods, the monthly data will be derived in the same way for each one-month period as for treatment phase. For patients who discontinued early during the post-treatment phase, if the date of discontinuation is within 30 days of previous visit date, all data between the previous visit date and the discontinuation date will go to one monthly period; if the date of discontinuation is more than 30 days of the previous

visit date, then the first 30 days will be the first monthly period, and the rest will be considered as part of the second monthly period.

This approach to missing ePRO diary data assumes that the rate of migraine headaches per day is the same for days with missing and non-missing ePRO diary days, and it is missing at random (MAR). The same approach will also be applied to secondary and exploratory efficacy measures that are derived from ePRO data.

Example 1: A patient has 64 days between Visit 13 and Visit 14. He completes the study on Visit 14. Then he has

- 1st half month = ePRO diary data from day 1 to day 32
- 2nd half month = ePRO diary data from day 33 to day 64.

Example 2: A patient has 64 days between Visit 13 and Visit 14. He discontinues the study on Visit 14 (i.e., disposition is not marked as completed). Then he has

- 1st half month = ePRO diary data from day 1 to day 30
- 2nd half month = ePRO diary data from day 31 to day 64.

Example 3: A patient has 70 days between Visit 13 and Visit 14 (outside of visit allowance). He completes the study on Visit 14. Then all data will be captured and he has

- 1st half month = ePRO diary data from day 1 to day 35
- 2nd half month = ePRO diary data from day 36 to day 70.

Example 4: A patient has 70 days between Visit 13 and Visit 14 (outside of visit allowance). He discontinues the study on Visit 14 (i.e., disposition is not marked as completed). Then all data will be captured and he has

- 1st half month = ePRO diary data from day 1 to day 30
- 2nd half month = ePRO diary data from day 31 to day 70.

Example 5: A patient has 35 days between Visit 13 and Visit 14. He discontinues the study on Visit 14 (i.e., disposition is not marked as completed). Then he has

- 1st half month = ePRO diary data from day 1 to day 30
- 2nd half month = ePRO diary data from day 31 to day 35.

Example 6: A patient has 14 days between Visit 13 and Visit 14. He discontinues the study on Visit 14 (i.e., disposition is not marked as completed). Then he has

- 1st half month = ePRO diary data from day 1 to day 14
- 2nd half month = No ePRO diary data

Example 7: A patient has 14 days between Visit 5 and Visit 6. He discontinues the study on Visit 6. Then he has

- Month 2= ePRO diary data from day 1 to day 14

Additionally, if the compliance rate for each monthly interval is ≤50%, then all endpoints to be derived from the ePRO diary data for that one-month period will be considered missing. For the post-treatment phase, the derived one-month periods (resulting from splitting two-month visit interval) will be treated similarly. For a patient who discontinued early in the double-blind treatment phase or post-treatment phase, the compliance rate for the last month of that study period will be calculated with the denominator of the maximum of 30 and the total number of calendar days in that month, i.e., max(30, the total number of calendar days in that month). For the rest of months and the period, the compliance rate will be calculated as described in Section 5.5.7.

In the Example 7 above, diary compliance rate for Month 2 is less than 50% even if he has no missing diary for 14 days between Visit 5 and Visit 6. Note that he discontinues and the denominator is max(30, 14) =30. Hence, diary compliance rate = 14/30 *100 < 50%. Hence Month 2 diary data is considered as missing.

Key/Other Secondary and Exploratory Efficacy Measures based on migraine headache and migraine acute treatment

The same approach to adjusting the number of days within each period to a 30-day period and the same approach to imputing monthly data based on compliance as for the primary measure will be applied to all efficacy measures that are derived from ePRO diary data and need normalization to 30-day period, including:

- **Number of ICHD migraine headache days** is calculated as the number of calendar days in a 30-day period on which a migraine occurs. Probable migraine is excluded.
- **Number of headache days** is calculated as the number of calendar days in a 30-day period on which a headache occurs.
- **Number of moderate to severe headache days** is calculated as the number of calendar days in a 30-day period on which a headache occurs with a moderate or severe severity.
- **Number of headache hours** is calculated as the total number of headache hours in a 30-day period on days when a headache occurred.
- **Number of migraine headache hours** is calculated as the total number of headache hours in a 30-day period on days when a migraine or probable migraine occurs.

- **Number of migraine headache days with abortive (acute) medication use** is calculated as the number of calendar days in a 30-day period on which migraine or probable migraine occurs and abortive (acute) medication is used.
- **Number of migraine attacks** per 30-day period is calculated as the number of sets of consecutive days with migraine or probable migraine separated by at least one migraine-free day. For example, a migraine or probable migraine starting on 5 JAN and ending on 6 JAN will result in a migraine/probable migraine-free day on 7 JAN (assuming that there is no migraine/probable migraine on 7 JAN). This will count as one migraine attack that started on 5 JAN and ended on 6 JAN. For a migraine attack that begins in one 30-day period but ends in another, only one migraine attack will be counted in the first of the two periods. For example, in the case of 7 days of consecutive migraine/probable migraine headache with 3 days in the baseline period and 4 days in Month 1, only one migraine attack will be counted in the baseline period; the 4 days of migraine/probable headache in Month 1 will not be counted as a migraine attack in Month 1.

Additional secondary and exploratory efficacy measures will be derived as follows:

- **Mean severity of remaining migraine or probable migraine headaches** on migraine headache days will be calculated at each period (including baseline and any post-baseline periods). For the calculation of mean severity, for days with migraine or probable migraine, severity varies from 1 to 3 with 1 = mild, 2 = moderate, and 3 = severe. The mean severity for each period will be calculated as:

$$\frac{\text{Sum of Severity of migraine headache days in the period}}{\text{\# of migraine headache days in the period}}$$

  For periods with zero migraine headache days, the mean severity is considered not applicable hence missing in the analysis data set.

- **Proportion of migraine headache days requiring medication use for abortive (acute) treatment** will be calculated at each period as:

$$\frac{\text{number of migraine headache days with abortive (acute) medication use}}{\text{number of migraine headache days in the period}}$$

  For periods with zero migraine headache days, the proportion would be missing.

- **Percent change from baseline in the number of migraine headache days** (used for responder analysis) will be calculated for any post-baseline 30-day period as:

$$-1 * \frac{100 \times (\text{\# of MHD in Month Y} - \text{\# of MHD in baseline period})}{\text{\# of MHD in baseline period}}$$

An **X% responder** is defined as Yes, if any patient who has a ≥X% reduction in the total number of migraine headache days in a 30-day period relative to baseline period, as No if otherwise. Therefore, if the percent change from baseline in the number of migraine headache days is ≥X%, the patient will be counted as an X% responder. In other words, if the response rate defined above in a month is ≥X%, then the patient will be an X% responder in that month. Indicators of X% responders will be derived for X=0, 5, 10, …, 95, and 100.

- **50% responders sustained for at least three consecutive months to patient's endpoint in the double-blind treatment phase in the number of monthly migraine headache days** is defined as meeting 50% responder criteria in the number of migraine headache days for three consecutive months to patient's endpoint in the double-blind treatment phase. Anyone else are non-responders, including those discontinued early within 3 months and those continued after 3 months but do not meet 50% response criteria for their last three months.
- **50% responders sustained for all six months during treatment phase in the number of migraine headache days** is defined as meeting the 50% responder criteria in the number of migraine headache days for Months 1-6 in the double-blind treatment phase. Anyone else are non-responders, including those who discontinued early and those who completed 6-month treatment phase but did not meet 50% response criteria for one or more of the 6 months.
- **Time to first 50% response (in months)** is defined as the first month when 50% response is met during the double-blind treatment phase (SP III). If a patient has not met a 50% response during SP III, they will be censored at the last month where the 50% response status is not missing.
- **Time to first loss of 50% response in the post-treatment phase (in months)** is calculated for Month 6 50% responders as the time from the end of treatment phase to the first month in Study Period IV at which these patients no longer meet the 50% response criteria. Patients who continue meeting the criteria until the end of the study will be censored.
- **Time to initiation of treatment with a migraine preventive medication (in days) in the post-treatment phase** is defined as the date of start of the migraine preventive medication (based on information collected from concomitant medication electronic case report form [eCRF]) in the post-treatment follow-up phase (SP IV) minus the last visit date of SP III. If a patient did not initiate preventive treatment during SP IV, they will be censored at the disposition date of SP IV. This analysis will be conducted only for patients who entered SP IV.
- **Number of migraine headache days with photophobia and phonophobia** is calculated as the total number of migraine headache days with an answer of "yes" to Question 7 in a 30-day period.

- **Number of migraine headache days with nausea and/or vomiting** is calculated as the total number of migraine headache days with an answer of "yes" to Question 8 in a 30-day period.
- **Number of migraine headache days with aura** is calculated as the total number of migraine headache days with an answer of "yes" to Question 12 in a 30-day period.
- **Number of migraine headache days with prodromal symptoms other than aura** is calculated as the total number of migraine headached days with an answer of "yes" to Question 13 in a 30-day period.

Other Efficacy Measures based on migraine headache and migraine acute treatment (not specified in Key/Other Secondary and Exploratory Efficacy Measures)

- **Number of non-migraine headache days with aura** is calculated as the total number of non-migraine headache days with an answer of "yes" to Question 12 in a 30-day period.
- **Proportion of aura among migraine attacks** is calculated as follows: 1) among all the migraine attacks, only if aura happened on the first day of migraine attack, it will be counted as migraine attack with aura; 2) then within each period, the proportion of aura among migraine attack is calculated as the total number of migraine attacks with aura divided by the total number of migraine attacks. If the denominator is zero, then the proportion is set to missing.

  Note: Some analysis listed below are based on combination medications. Combination medications (such as aspirin/acetaminophen/caffeine) will be counted in each medication category that applies (such as NSAIDs/aspirin and acetaminophen/paracetamol).

- **Number of days with abortive medication use** is calculated as the number of calendar days in a 30-day period on which an abortive medication is used.
- **Number of classes of abortive medications** is calculated as the total number of classes of abortive medications during a 30-day period.
- **Number of classes of abortive medications used on migraine headache days** is calculated as the total number of classes of abortive medications taken on migraine headache days during a 30-day period.
- **Average number of classes of abortive medication use per day** is calculated as follows for each monthly period:

$$\frac{\sum_{i=1}^{5} i * n_i}{\sum_{i=0}^{5} n_i}$$

Where n_i denotes the number of days during a monthly period with i class(es) of abortive medication use, and $i = 0,1,..,5$. Note that $\sum_{i=0}^{5} n_i$ =# of non-missing (and complete) diary days for the period.

- **Average number of classes of abortive medications used per migraine headache day** is calculated as follows for each period:

$$\frac{\sum_{i=1}^{5} i * m_i}{\sum_{i=0}^{5} m_i}$$

Where m_i denotes the number of migraine headache days during a period with i class(es) of abortive medication use, and $i = 0,1,..,5$. If the denominator is zero (i.e., no MHD in the period), then the average is set to missing.

- **Number of days with triptans use** is calculated as the number of calendar days in a 30-day period on which triptan is used.
- **Number of migraine headache days with triptans use** is calculated as the number of migraine headache days in a 30-day period on which triptan is used.
- **Number of days with NSAIDs/aspirin use** is calculated as the number of calendar days in a 30-day period on which NSAIDs/Aspirin is used.
- **Number of migraine headache days with NSAIDs/aspirin use** is calculated as the number of migraine headache days in a 30-day period on which NSAIDs/aspirin is used.
- **Number of days with acetaminophen/paracetamol use** is calculated as the number of calendar days in a 30-day period on which Acetaminophen/paracetamol is used.
- **Number of migraine headache days with acetaminophen/paracetamol use** is calculated as the number of migraine headache days in a 30-day period on which acetaminophen/paracetamol is used.
- **Number of days with ergots use** is calculated as the number of calendar days in a 30-day period on which ergots are used.
- **Number of migraine headache days with ergots use** is calculated as the number of migraine headache days in a 30-day period on which ergots are used.
- **Number of days with anti-nausea use** is calculated as the number of calendar days in a 30-day period on which anti-nausea is used.
- **Number of migraine headache days with anti-nausea use** is calculated as the number of migraine headache days in a 30-day period on which anti-nausea is used.

- **Number of days with multiple class medication use** is calculated as the number of calendar days in a 30-day period on which multiple class medication is used. Multiple class medication use is defined as using at least two classes of the following 5 classes on a day: triptans, NSAIDs/aspirin, acetaminophen/paracetamol, ergots, anti-nausea.
- **Number of migraine headache days with multiple class medication use** is calculated as the number of migraine headache days in a 30-day period on which multiple class medication is used. Multiple class medication use is defined as using at least two classes of the following 5 classes on a day: triptans, NSAIDs/aspirin, acetaminophen/paracetamol, ergots, anti-nausea.

- **Number of migraine headache days with menstrual period** is calculated as the total number of migraine headache days with an answer of "yes" to Question 9 in a 30-day period. (Note: The analysis population is based on **female who have at least one "Question 9 =Yes" through the entire study in CGAN.**
- **Number of days with abortive medication use on non-headache days** is calculated as the number of calendar days in a 30-day period on which an abortive medication is used and "Question 1 = No".

The following analysis is based on weekly data:

- **Number of weekly migraine headache days in Month 1** is calculated as the number of migraine headache days in a 7-day period on which a migraine headache occurs. At Month 1, the first 7 calendar days will be counted as week 1, the second 7 calendar days will be counted as week 2, the third 7 calendar days will be counted as week 3, the rest of the calendar days (up to Visit 5 – 1 day) will be counted as week 4. If diary is missing on a certain day, then it is counted as non MHD day. If patients discontinues early, then the rest of the days are considered non MHD day.

  Example: Suppose duration of Visit 3 (2018/Jan/1) and Visit 5 (2018/Jan/31) is 30 days. Then duration of week 4 is 9 days with Jan/22, Jan/23,…, Jan/30. Note that Jan/31 is counted for Month 2.

5.4.2. Other Efficacy Measures

5.4.2.1. Patient Global Impression

5.4.2.1.1. PGI-S (Patient Global Impression of Severity)

The Patient Global Impression of Severity (PGI-S) will be collected at baseline and monthly post-baseline visits (Month 1, Month 2,…, Month 6) in SP III and visit 14 (Month 10) in SP IV. In this single-item scale, patients rate the severity of their migraine condition on a scale ranging from "not at all ill"(coded as 1) to "extremely ill" (coded as 7).

PGI-S responder at each visit is defined as having a severity decrease from baseline of at least 2 points on the 7-point scale at the specific visit. The model estimates mean percentages of patients meeting this definition of response over the final 3 months of double-blind treatment (average of Months 4 to 6).

5.4.2.1.2. PGI-I (Patient Global Impression of Improvement)

CCI

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5.4.3. Quality of Life Questionnaires

5.4.3.1. Migraine Specific Quality of Life (MSQ) v2.1

Migraine Specific Quality of Life (MSQ) v2.1 consists of 14 questions. The questions measure the impact of migraine on health-related quality of life across three domains: 1) Role Function-Restrictive (7 questions), examines the degree to which performance of daily activities is limited by migraine; 2) Role Function-Preventive (4 questions), examines the degree to which performance of daily activities is prevented by migraine; 3) Emotional Function (3 questions), examines feelings of frustration and helplessness due to migraine.

Precoded item values and final item values for each MSQ item response are shown in Table CGAN. 5.3. All item values range from 1 to 6. Final item value will be used as for analysis with higher score reflecting better quality of life.

Table CGAN. 5.3 Item Values for Migraine Specific Quality of Life (MSQ) Item

Response Categories	Precoded Item Value	Final Item Value
None of the time	1	6
A little bit of the time	2	5
Some of the time	3	4
A good bit of the time	4	3
Most of the time	5	2
All of the time	6	1

Questions 1 to 7 of the questionnaire will be grouped together as Role Function-Restrictive domain, questions 8 to 11 as Role Function-Preventive domain, and questions 12 to 14 as the Emotional Function domain.

The score of each domain will be calculated as the sum of the final item values of each question in that domain, using imputed scores where applicable.

When the number of missing items is fewer than or equal to 3 for the Role Function-Restrictive domain, the value of missing item(s) can be estimated using the average of the other completed items within the same domain. Similarly, when the number of missing items is fewer than or equal to 2 for the Role Function-Preventive, and fewer than or equal to 1 for the Emotional Function dimension, the value of missing item(s) can be estimated using the average of the other completed items within the same domain.

If the number of missing responses was more than half the questions in a domain, meaning that imputation of missing scores will not be done, then the score for that domain will not be calculated, hence set as missing.

The total score of all three domains will be calculated as the sum of raw scores of three domains. If any of the three domain scores is missing, then total score will be missing.

In addition, the raw scores of each domain and the total score will be transformed to a 0 to 100 scale using the following formulae:

- Role Function-Restrictive (range of 7 to 42):

$$\frac{(\text{raw score} - 7)\text{x}100}{35}$$

- Role Function-Preventive (range of 4 to 24):

$$\frac{(\text{raw score} - 4)\text{x}100}{20}$$

- Emotional Function(range of 3 to 18):

$$\frac{(\text{raw score} - 3)\text{x}100}{15}$$

- Total Score (range of 14 to 84):

$$\frac{(\text{raw total score} - 14)\text{x}100}{70}$$

The MSQ Role Function-Restrictive domain responder is defined as patients with the change from baseline sub score >=25 (average of Month 4, 5, and 6). If one or two months are missing for the domain, then take the average from the existing months' domain. If all months (Month 4, 5, and 6) are missing then the response value is set to missing.

5.4.3.2. MIDAS (Migraine Disability Assessment) Questionnaire

The Migraine Disability Assessment questionnaire (MIDAS) consists of 5 questions (Q1-Q5) and two additional questions (A and B). The questionnaire measures the impact that migraine headaches have on migraineurs' life, including days of work or school missed, days with productivity at work or school reduced to half or more, days with household work missed, days with productivity in household work reduced to half or more, and days missed family / social / leisure activities. Each question is answered as a numeric number of days during the past 3 months of assessment, ranging from 0 to 90. The answers to all 5 questions will be added up to a total MIDAS score. No imputation is needed when calculating the total score as patients are not allowed to send partial data.

The MIDAS responders are defined as patients with ≥50% improvement in the total MIDAS score.

The total MIDAS score, the raw score of each question, and the indicator of MIDAS responders will be used as analysis values.

5.4.3.3. HCRU (HealthCare Resource Utilization and Employment Status) Questionnaire and employment status

The Healthcare Resource Utilization (HCRU) will be solicited by study personnel while documenting patient responses. The HCRU consists of 3 questions;

1. Hospital emergency room visits since your last study visit (YES/NO)
    a. If yes, how many times did you go to a hospital emergency room?
    b. How many of these times going to a hospital emergency room were related to your migraine headaches?
2. Overnight stays as a patient in a hospital since your last study visit (YES/NO)
    a. If yes, how many different times were you as a patient in a hospital overnight?

- How many days total were you in the hospital for overnight stay?

b. How many of these times, as a patient in a hospital overnight, were related to your migraine headaches?
c. How many days total, as a patient in a hospital overnight, were related to your migraine headaches?

3. Any other visits with a healthcare professional that occurred since your last study visit (YES/NO)
    a. If yes, how many different times did you visit a healthcare professional?
    b. How many of these times, visiting a healthcare professional, were related to your migraine headaches?

Regarding question 3, patients are specifically asked about the number of healthcare events that are related to migraine headaches, outside of visits associated with their participation in the clinical trial.

The baseline visit will include the same questions, however, with the frame of reference being over the last 6 months.

A question on employment status is also solicited, given the correlation and potential confounding with health outcomes measures. More specifically, one of the following statuses with additional information will be recorded.

- Working for pay
    - average number of hours worked (hours/week)
    - how long has the patient had this job? (number of weeks)
- Student
- Keeping house (full-time)
- Volunteer work
    - average number of hours volunteered (hours/week)
- Unemployed, *not* due to study disease disability
- Unemployed, due to study disease disability
- Retired
- Self-employed

There will be no imputation for missing values.

5.4.3.4. PSMQ-M (Patient Satisfaction with Medication Questionnaire-Modified) Questionnaire

The Patient Satisfaction with Medication Questionnaire-Modified (PSMQ-M) is a self-rated scale which measures patients' levels of satisfaction with study medication (Kalali 1999). The scale has been modified for use in this study, assessing 3 items related to the clinical trial treatment over the past 4 weeks: satisfaction, preference, and side effects.

Satisfaction responses range from "very unsatisfied" to "very satisfied" with the current treatment (5 categories).

Preference compares the current study medication to previous medications, with responses from "much rather prefer my previous medication" to "much rather prefer the medication administered to me during the study" (5 categories).

The side effects responses range from "significantly less side-effects" to "significantly more side-effects" (5 categories).

Positive response for each item are defined as follows:

- Satisfaction : "Very satisfied" or "Somewhat Satisfied"
- Preference : "Much Prefer Study Medication" or "Prefer Study Medication"
- Side Effects: "Much Less Side Effects" or "Less Side Effects"

The PSMQ-M will be collected at Month 1 and Month 6.

5.4.4. Safety Endpoints

Safety endpoints consist of the incidences of treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and adverse events (AEs) leading to discontinuation, follow-up-emergent adverse events (FEAEs) during Study Period IV, vital signs (blood pressure, pulse, and body temperature), weight, suicidal ideation and behaviors assessed by solicited questioning using the Columbia-Suicide Severity Rating Scale (C-SSRS), electrocardiograms (ECGs), and laboratory measures (chemistry, hematology, and urinalysis).

5.4.5. Immunogenicity Endpoints

Immunogenicity endpoints consist of the incidences of anti-drug antibodies (ADAs) in all trial participants at baseline (pre-existing ADAs), and in all trial participants at post-baseline (treatment emergent ADAs). An additional endpoint is the incidence of neutralizing antibodies (NAbs) present in those trial participants with ADAs.

5.4.7. Pharmacokinetic Assessment

Serum LY2951742 concentration will be determined in trial participants following LY2951742 administration at specified visits throughout the trial. Pharmacokinetic assessments will be summarized in the PK/PD analysis plan described in the protocol.

5.5. Statistical Analyses

The SAP Version 1 was approved prior to first patient visit and SAP Version 2 prior to any unblinding of the study team. The SAP supersedes the statistical plans described in the protocol.

5.5.1. General Considerations

Unless otherwise specified, analyses will be conducted on an intent-to-treat (ITT) population, which will include all patients who are randomized at Visit 3 and receive at least 1 dose of study drug. Patients in the ITT population will be analyzed according to the treatment group to which they are randomized. When change from baseline is assessed, the patient will be included in the analysis only if he/she has a baseline and a post-baseline measurement.

Unless otherwise specified, hypothesis tests will be based on two-sided alpha level of 0.05. Ninety-five percent confidence intervals (CIs) for the difference in least-square means (LSMeans) between treatment groups (LY2951742 and Placebo) will be provided.

For the primary analysis (overall mean change from baseline during the 6-month double blind period), multiplicity adjustment (120 mg versus placebo and 240 mg versus placebo), step-down Dunnett procedure, will be used.

Change from baseline of continuous variables with repeated measures will be analyzed using a mixed model repeated measures (MMRM) analysis. An MMRM analysis refers to a restricted maximum likelihood (REML)-based, mixed-effects repeated measures analysis using all the longitudinal observations at each post-baseline visit.

In addition to the MMRM approach, sensitivity analysis of covariance (ANCOVA) model using the last observation carried forward (LOCF) to account for missing data will be conducted to provide additional information for the primary analysis.

For other continuous variables without repeated measures, the change from baseline to LOCF endpoint will be analyzed using an analysis of variance (ANOVA) or ANCOVA model.

Unless otherwise specified, when an ANOVA model or ANCOVA model is used to analyze a continuous efficacy variable, type III sum-of-squares for the least-squares means (LSMean) will be used for the statistical comparisons.

Visit-wise binary efficacy variables will be analyzed using a generalized linear mixed model (GLIMMIX) as pseudo-likelihood-based mixed effects repeated measures analysis for categorical data (MMRM-CAT).

For categorical efficacy variables without repeated measures, comparisons between treatment groups will be performed using logistic regressions (see Section 5.5.1.1 for details).

For other categorical variables without repeated measures, comparisons between treatment groups will be performed using Fisher's exact tests unless otherwise specified. For example,

- Baseline patient characteristics
- Safety measures (including percentages of patients with TEAEs, SAEs, and AEs reported as a reason for discontinuation, as well as those patients who met categorical criteria for changes in vital signs and weight, ECGs, and laboratory tests)

Only scheduled visit data will be available for the following data. In other words, there will be no unscheduled visit data;

- Patient migraine headache data collected by ePRO diary
- PGI-S
- PGI-I
- MSQ v2.1
- MIDAS
- PSMQ-M
- HCRU

For details of analysis methods, please refer to the following sub-sections.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the changes, will be described in the statistical analysis plan and/or in the clinical study report.

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

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

Post-Treatment Emergent and Follow-up Emergent are used interchangeably in this study.

Efficacy analysis baseline related values are based on eligibility day derived from ePRO data, not IWRS data (see Section 5.4.1 for the eligible day definition).

Summary tables will display each arm (placebo, LY120, LY240). In addition, if the summary is sorted by LY_All arm (LY120 and LY240 combined), then LY_All will also be shown (e.g. summary of TEAE). For some baseline characteristic values (e.g. previous prevention therapy), frequencies will be sorted by "total" (placebo, LY120, and LY240 combined) and "total" will be also displayed.

The measurements of PGI-I, PGI-S, MSQ, MIDAS PSMQ-M, or HCRU will be used if they are taken on the same day of the injection date even if the measurements are after injection timing. But if it is after the injection day, then it will be excluded.

Unless otherwise specified, SPIII and SPIV combined analysis will be performed only for the primary and the key secondary analysis. That is,

- Mean change from baseline in the number of MHD
- The proportion of patients with reduction from baseline ≥50%
- The proportion of patients with reduction from baseline ≥75%
- The proportion of patients with reduction from baseline =100%
- Mean change from baseline in the Role Function-Restrictive domain score of MSQ
- Mean change from baseline in the number of MHD requiring medication for the acute treatment of migraine
- Mean change from baseline in PGI-S

For PGI-I, PGI-S, and MSQ analysis with repeated measurement in SP III (both continuous and binary outcomes), both average of month 4 to month 6 and overall (month 1 to month 6) will be shown for treatment comparisons.

5.5.1.1. Adjustments for Covariates

Unless otherwise specified (e.g. PGI-I analysis), the MMRM models will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariates of baseline value and baseline-by-month interaction. The baseline value and baseline-by-month interaction are included to account for the differential influence over time that the baseline value has on the post-baseline values.

Except for efficacy analyses on migraine headache days, the baseline number of MHD (<8, >=8) is added as a categorical covariate for the MMRM model specified above.

When an ANCOVA model is used to analyze a continuous efficacy or safety variable at LOCF endpoint, the model will contain the main effects of treatment, and appropriate baseline value (baseline of the response variable) as a covariate.

When ANCOVA is used for the primary endpoint, Month 1 to Month 6 values are imputed first using for any missing data by LOCF. Then the change from baseline for overall period (Month 1 to Month 6) is calculated as the average of change from baseline to Month 1, change from baseline to Month 2, …, change from baseline to Month 6. The statistical model contains treatment effect and baseline MHD value (continuous). Statistical tests for treatment effect (LY120 vs. placebo, or LY240 vs. placebo) are based on the main effect of the treatment.

The GLIMMIX models for the repeated binary outcomes will include the fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value. In addition, the baseline number of MHD (<8, >=8) is added as a categorical covariate except for categorical analysis of response rate (such as 20% response rate) derived from migraine headache days where the continuous value of baseline migraine headache days will be used as covariate.

For example, consider MHD 50% responder analysis. "The continuous, fixed covariate of baseline value" equals to (continuous) MHD at baseline (Month 0) because MHD 50% responder is derived from (continuous) MHD at each month. The baseline value-by-month interaction will be excluded from the model in order to increase the likelihood of convergence.

For example, MIDAS 50% responder at month 6 analysis, the baseline number of MHD (<8, >=8) is added as a categorical covariate for the GLIMMIX model specified above.

For example, PGI-S responder analysis (based on average of month 4, month 5, and month 6), the model includes treatment, month, treat*month, baseline (PGI-S) and the baseline number of MHD (<8, >=8).

When a logistic regression is used to analyze a binary variable, the model will include the main effect of treatment, and appropriate baseline value as a covariate.

- For MSQ Role Function-Restrictive responder (change from baseline >=25) analysis, the baseline number of MHD (<8, >=8) and baseline score of MSQ Role Function-restrictive are added as covariates.
- For positive response analysis in PSMQ-M, the baseline number of MHD (<8, >=8) is added as a categorical covariate
- For maintenance of 50% response analysis for the last 3 months or 6 months, the baseline MHD (continuous) is added as a covariate.

For time to event analysis of 50% response (such as Time to first 50% response in double-blind treatment phase and Time to first loss of 50% response in post-treatment phase), stratified log

rank test will be used with the baseline number of MHD category (<8 vs >=8) as the stratification factor and the treatment as the covariate.

5.5.1.2. Handling of Dropouts or Missing Data

Two statistical approaches to handling missing data will be used as appropriate: repeated measures analyses and ANCOVA.

For the repeated measures analyses, the model parameters are simultaneously estimated using restricted likelihood estimation incorporating all of the observed data. Estimates have been shown to be unbiased when the missing data are MAR.

For ANCOVA model, response values at each visit will be imputed by LOCF first, then the average of 6 months (double blind period) for the response value will be derived. (Section 5.5.1.1).

Please refer to Section 5.4.1 for general approach to handling missing diary data for derivation of the number of migraine headache days and other efficacy measures (some exceptions: migraine attacks) derived from ePRO data.

Approaches to Handling Missing Diary Data for the Derivation of Migraine Attack

For the analysis of migraine attack, the LOCF method will be used to impute the missing ePRO diary days. In other words, if the patient was migraine headache free on the day before the missing ePRO diary day, this would be carried forward as no migraine headache day until the actual next non-missing call day. On the other hand, if the day before the missing diary day is a migraine headache day, then it would be carried forward as migraine headache day until the next non-missing diary day. The imputation will be carried out for all the missing diary days between the first non-missing to the last day during that period.

If the compliance rate for a monthly interval is ≤50%, the number of migraine attacks during that month will be considered missing. Please refer to Section 5.4.1 and Section 5.5.7 for compliance rate calculation.

5.5.1.3. Analysis Populations

Analysis populations are defined below:

All Patients: All patients who signs informed consent.

All Randomized Patients (ARP): All patients who are randomized at Visit 3.

Intent-to-Treat (ITT) Population: All patients who are randomized at Visit 3 and received at least one dose of the study drug. Patients in the ITT population will be analyzed according to the treatment that they were randomized to. Unless otherwise specified, the ITT population will be the primary population on which statistical analysis will be performed.

Post-treatment Population: All patients who entered the post-treatment phase (Study Period IV) as indicated by entering any post-treatment visit. Patients in the post-treatment population will be analyzed according to the treatment that they were randomized to at Visit 3. Post-treatment Population is a subset of ARP.

ADA Follow-up Cohort: All patients who are post-treatment population and have both baseline and at least one postbaseline ADA assessment during SP IV.

Per Protocol Set (PPS): Intent-to-treat population who has no important protocol deviation which impacts efficacy analysis. Details will be specified in Section 5.5.3.

Safety Population: This is the same as the ITT population except the assigned arm definition. It is determined by modal treatment the patient received during the double-blind treatment period (up to the injection visits if they discontinue early). For determining modal treatment, do not consider the loading dose visit for patients assigned to an LY120-mg treatment group, but do consider it for patients assigned to the placebo and LY240-mg treatment groups. If there are 2 or more modes, then add the loading dose visit and recalculate the mode. If there is still a tie, the highest dose of the modes is to be used.

Example 1: Suppose a patient, randomized as LY120-mg treatment group, discontinues at Visit 5 (Month 1) who has LY 240-mg loading dose at Visit 3 (Month 0) and no dose at Visit 5 (Month 1). It implies mode is not unique, because Visit 3 dosing is omitted. Its mode is 0mg, 120mg, 240mg (counted as zero at each dose). Then the patient is assigned to LY240-mg arm group (the highest dose) as safety population.

Example 2: Suppose a patient, randomized as LY120-mg treatment group, discontinues at Visit 6 (Month 2) who has LY 240-mg loading dose at Visit 3 (Month 0), LY 120-mg dose at Visit 5 (Month 1) and no dose at Visit 6. Then the patient is assigned to LY120-mg arm group as safety population.

PPS is used for a sensitivity analysis on the primary efficacy analysis.

Unless otherwise specified, safety population is used for safety analysis and exposure.

Unless otherwise specified, statistical analysis for efficacy will be carried out for 6 months treatment phase (Study Period III), 4 months post-treatment phase (Study Period IV), and/or 6 months treatment and 4 months post-treatment phase combined (Study Period III /IV) based on following population:

- For the analyses in Study Period III, the **ITT population** will be used.
- For the analyses in Study Period III/IV, the **ITT population** will be used.
- For the analyses in Study Period IV, the **post-treatment population** will be used.

5.5.1.4. Baseline and Post-Baseline Definition

Table CGAN. 5.4 describes the rules for determining the patient population and baseline and post-baseline observations for each study phase and type of analysis. When "last of Visit x-x" is used in the table, the last nonmissing observation obtained in the visit interval will be used.

Table CGAN. 5.4 Patient Population with Baseline and Post-Baseline Definitions by Study Period and Type of Analysis

Study Period / Analysis	Patient Population	Baseline Observation	Post-baseline Observation(s)
Study Period III			
Primary / Secondary / Exploratory efficacy analyses (Repeated Measures)	ITT Population with a baseline and at least one post-baseline observation	Visit 3	All Visits 3.01–12
Primary efficacy analyses (Repeated Measures)	PPS with a baseline and at least one post-baseline observation	Visit 3	All Visits 3.01–12
Primary / Secondary / Exploratory efficacy analyses at LOCF endpoint or for average of observed monthly values	ITT Population with a baseline and at least one post-baseline observation	Visit 3	Visit 3.01-12
Quality of Life analyses (Repeated Measures)	ITT Population with a baseline and at least one post-baseline observation	Visit 3	All Visits 3.01–12
Quality of Life analyses at LOCF endpoint or for average of observed monthly values	ITT Population with a baseline and at least one post-baseline observation	Visit 3	Visit 3.01-12
TEAEs	Safety Population	All Visits 1–3. Pre-existing condition that is still ongoing at Visit 1 should be evaluated as baseline values.	All Visits 3.01–12
Serious Adverse Events, Discontinuations due to Adverse Events	Safety Population	NA	All Visits 3.01–12
C-SSRS categorical analyses	Safety population with a baseline and at least one post-baseline C-SSRS assessment	Recent History: All Visits 1–3 excluding lifetime[a] All Prior History: Visits 1 – 3 including lifetime[a]	All Visits 3.01–12
Treatment emergent abnormal laboratory values	Safety Population with normal laboratory values at all nonmissing baseline visits (with respect to direction being analyzed) and who have at least one post-baseline observation	All Visits 1–3	All Visits 3.01–12
Treatment emergent immunogenicity	Safety Population, ADA follow-up cohort (See Section 5.5.12.1.6)	Visit 3	All Visits 3.01–12
Treatment emergent changes in vital signs, weight,	Safety Population with a baseline and at least one	Low:	Low:

Study Period / Analysis	Patient Population	Baseline Observation	Post-baseline Observation(s)
and ECGs	post-baseline observation	Minimum value from Visits 1–3 High: Maximum value from Visits 1–3	Minimum value from Visits 3.01–12 High: Maximum value from Visits 3.01–12
Continuous safety analyses (Repeated Measures)	Safety Population with a baseline and at least one post-baseline observation	Last of Visits 1–3	Scheduled visits: 3< Visits <=12
Continuous safety analyses – change from baseline to LOCF endpoint (ANCOVA)	Safety Population with a baseline and at least one post-baseline observation	Last of Visits 1–3	Last scheduled visit: 3< Visit <=12
Study Period III and IV combined			
Primary / Key Secondary efficacy analyses	ITT Population with a baseline and at least one post-baseline observation	Visit 3	All Visits 3.01-14
Quality of Life analyses	ITT Population with a baseline and at least one post-baseline observation	Visit 3	All Visits 3.01-14
Continuous safety analyses (Repeated Measures)	Safety Population with a baseline and at least one post-baseline observation	Last of Visits 1—3	All Visits 3.01-14
Treatment emergent immunogenicity	Safety Population, ADA follow-up cohort (See Section 5.5.12.1.6)	Visit 3	All Visits 3.01–14
Study Period IV			
Continuous safety analyses – change from baseline to LOCF endpoint (ANCOVA)	Post-treatment Population with a baseline and at least one post-baseline observation	Last of Visits 1-12	Last Visit: 12.01-14
FEAEs	Post-treatment Population	All Visits 1- 12. Pre-existing condition that is still ongoing at Visit 1 should be evaluated as baseline values.	All Visits 12.01–14
Serious Adverse Events, Discontinuations due to Adverse Events	Post-treatment Population	NA	All Visits 12.01–14
Follow-up emergent abnormal laboratory values	Post-treatment Population with normal laboratory values at all nonmissing baseline visits (with	All Visits 1- 12	All Visits 12.01–14

Study Period / Analysis	Patient Population	Baseline Observation	Post-baseline Observation(s)
	respect to direction being analyzed) and who have at least one post-baseline observation		
Follow-up emergent changes in vital signs, weight and ECGs	Post-treatment Population with a baseline and at least one post-baseline observation	Low: Minimum value from Visits 1–12 High: Maximum value from Visits 1–12	Low: Minimum value from Visits 12.01–14 High: Maximum value from Visits 12.01–14
C-SSRS categorical analyses	Post-treatment Population with a baseline and at least one post-baseline C-SSRS assessment	Recent History: All Visits 1–12 excluding lifetime[a] All Prior History: Visits 1 – 12 including lifetime[a]	All Visits 12.01–14

Abbreviations: ADA = Anti-Drug Antibody; ANCOVA = analysis of covariance; C-SSRS = Columbia Suicide Severity Rating Scale; FEAE = follow-up emergent adverse event; ITT = intent-to-treat; LOCF = last observation carried forward; PPS = per protocol set; TEAE = treatment emergent adverse event.

Note: Visit 3.01 indicates the first unscheduled visit occurring after Visit 3 and prior to Visit 4. Visit 12.01 indicates the first unscheduled visit occurring after Visit 12 and prior to Visit 13. For efficacy and quality of life measures without unscheduled visits data point, Visit 3.01 indicates scheduled collection visits after visit 3.

[a] Lifetime is captured in the C-SSRS visit 1 CRF.

5.5.2. Patient Disposition

The number of ITT patients who complete the study or discontinue early will be tabulated for all treatment groups for Study Period III and Study Period IV separately, both overall and by visit. Reasons for discontinuation will be compared between treatment groups using Fisher's exact test for study period III with the ITT population. Descriptive statistics only will be presented for the treatment groups in Study Period IV with post-treatment population. Subcategories of discontinuation due to subject decision will be summarized too.

Listing of Subjects who discontinued for SP III or SP IV will be created for ITT population.

Patient allocation by investigator site will be summarized (the number of screened, randomized, discontinued from SP III, entered for SP IV, discontinued from SP IV, entered CGAP study) for all patients.

Summary of Reasons for Screen Failure will be created for all screen failure patients.

Listing of Detailed Reasons for Screen Failure will be created for all screen failure patients.

Listing of Patient population (e.g. PPS, safety population) by treatment will be created for all study periods for ITT population.

5.5.3. Important Protocol Deviations

Listings of subjects with important protocol deviations will be provided for ITT population. The following list of important protocol deviations will be determined before DBL. Detail criteria and methods will be specified in a separate document which also specify exclusion of PPS/ITT/safety population:

- Violation of informed consent :(e.g. Lack of informed consent or late informed consent)
- Serious Adverse event not reported
- Deviation related to inclusion/exclusion criteria
- Deviation of the rescreen criteria
- Deviation of the operation of Visit
- Deviation of the discontinuation criteria
- Deviation of study treatment dosing
- Deviation of concomitant drug and therapy
- Other important protocol deviations as determined by the Lilly clinical/medical group

Summary of important protocol deviations will be created for each arm and overall. The summary will be made for

- Baseline and SP III
- SP IV

Listing of Important Protocol Deviations (include flags whether affected to PPS/ITT/safety or not) will be made for

- Baseline and SP III
- SP IV

5.5.4. Patient Characteristics

The following patient characteristics at baseline will be summarized by treatment group for ITT patients.

- Demographic (age, gender, race and subrace, height, weight, body mass index, Age [<20, >=20])

  Note: body weight (as well as BMI) is based on the last observation before Visit 3 injection.

- Baseline MHD category per 30 day (<8, >=8) (Visit 2 to Visit 3) (by ePRO)
- Years since migraine diagnosis
- Migraine and headache related measures (e.g. number of non-MHD with aura, number of migraine headache days with Criteria C), and acute treatment related measures (e.g. number of MHD with triptans use, number of days with triptan use) per 30-day baseline period (Visit 2 to Visit 3) used for secondary and other efficacy measures as listed in
- PGI-S,
- MIDAS (total, each question)
- MSQ (total, 3 sub scores)
- Previous migraine prevention treatment (Yes, No, Yes and did not fail, Yes and fail >=1, Yes and fail >=2) (Visit 1)
- Number of previous migraine prevention treatment fail (Visit 1)
- Past usage (yes/no) or current usage (yes/no) of followings: Alcohol, caffeine, nicotine replacement therapy, and tobacco and nicotine combined

  Note: Except caffeine, summaries are based on patients with ≥20 years old.

- Medical history (except primary medical conditions). Medical history is defined as illness(es) that ended prior to the signing of informed consent. It will be summarized by preferred term (PT).

- Pre-existing condition (Visit 1). Pre-existing conditions are those AEs existing at Visit 1. It will be summarized by preferred term (PT).

- Number of Comorbid conditions other than migraine. Comorbid conditions other than migraine are those AEs existing before Visit 3 and continuing after Visit 3 other than migraine. (i.e., not contained "migraine" as PT). If it ends on Visit 3, then it is not a comorbid condition. The count is based on PT. (2 events with different LLT but the same PT will be counted as one comorbid condition.)
- Some other baseline variables used for the subgroup analysis in Table CGAN. 5.8:
    - Having aura or not at baseline (Yes/No) (Visit 2 to Visit 3)
    - Baseline ADA status (Yes/No) (Visit 3)
    - Baseline body weight (weight <= median, median < weight).

Baseline MHD difference by IWRS and ePRO eligibility day will be summarized. Its listing will be created.

Comparisons between treatment groups will be performed using Fisher's exact test for categorical data and ANOVA with treatment as independent variables in the model for continuous data.

Listing of Subjects Demographic will be created.

5.5.5. Exposure to Investigational Product

Patients will receive the investigational medicinal product (IMP) at the following planned time points:

- Beginning of Month 1 (Visit 3)
- Beginning of Month 2 (Visit 5)
- Beginning of Month 3 (Visit 6)
- Beginning of Month 4 (Visit 7)
- Beginning of Month 5 (Visit 8)

- Beginning of Month 6 (Visit 10)

The following will be derived from the information recorded on the eCRF:

- For treatment phase (SP III), duration of exposure in days is calculated as treatment phase last visit date – first date IMP administered + 1.
- For treatment phase (SP III), number and percentage of patients with 1, 2, 3, 4, 5, or 6 doses injected.

Comparisons between treatments for duration of IMP exposure will be performed using an ANOVA with treatment in the model. Number of patients with 1 dose, 2, 3, 4, 5 or 6 doses injected will be compared between treatment groups with the Fisher's exact test.

Listing of Subjects with Exposure to Investigational Product will be created.

Listing of treatment exposure with package number and internal lot number will be created.

5.5.6. Treatment Compliance

Treatment compliance will be calculated for Study Period III as:

$$\frac{\text{number of completed scheduled dosing visits in which the patient received 2 injections} * 100}{\text{number of completed scheduled dosing visits, including any skipped dosing visits before the last dosing visit (Visit 10, inclusive) or early discontinuation visit (exclusive)}}$$

Comparisons between treatments for treatment compliance will be performed using an ANOVA with treatment in the model. For this analysis, a partial dose (for example, a patient only got one injection instead of two) will be considered as no dose received.

5.5.7. Electronic Patient Reported Outcomes Diary Compliance

Electronic patient reported outcomes diary compliance at each month period and for overall will be calculated:

- SP III: baseline, Month 1,…, Month 6, overall (Month 1 through Month 6) for ITT population
- SP IV: Month 7,…, Month 10, overall (Month 7 through Month 10) for post treatment population

Diary compliance at each period is calculated as:

$$\frac{\text{Actual number of diary days in the period}}{\text{Expected number of diary days in the period}} * 100$$

Expected number of Diary days for baseline is calculated as date when a patient becomes eligible day minus date of Visit 2+1 (diary for Visit 2, diary for Visit 2+1,…, diary for eligible day).

For each patient, overall diary compliance for SP III is average of monthly compliance in SP III (Month 1,…, Month 6). If he discontinues early, then ignore the rest of the month. In this case, the last month compliance is based on max(30, the total number of calendrer days in that month) (See Section 5.4.1)

Expected number of Diary days for Month 7, Month 8, Month 9, and Month 10 in SP IV is calculated similarly. Note that 2-month visit interval (e.g. Month 7 and Month 8) will be split into two one-month interval as defined in Section 5.4.1. The section explains how to handle early discontinuation case.

For each patient, overall diary compliance for SP IV is average of monthly compliance in SP IV (Month 7,…, Month 10). If he discontinues early, then ignore the rest of the month. In this case, the last month compliance is based on max(30, the total number of calendrer days in that month) (See Section 5.4.1)

Example: Expected number of diary days in the period Month 3 = date of Visit 7 – date of Visit 6 (diary for Visit 6, diary for Visit 6+1 day, …, diary for Visit 7-1 day.)

In addition following will be summarized for each month and for overall:

- subjects with >=80% compliance
- subjects with >=50% compliance

Treatment comparisons for diary compliance for each month and for overall will be performed separately using an ANOVA with treatment in the model.

5.5.8. Previous Migraine Prevention Therapy and Previous Migraine Acute Treatment

The proportion of patients who received previous migraine prevention therapy, and the proportion of patients with response to the previous migraine prevention therapy within each of the 6 categories (to enter this trial, medical history event, adequate response, inadequate response, no response, and treatment availability) will be summarized for ITT patients. Treatment group comparisons will be done using the Fisher's exact test.
Previous migraine prevention therapies are migraine prevention therapies that started prior to the date of the first injection and stopped prior to or at the date of first injection which has indication recorded in the CRF (prior therapy migraine medication, or concomitant medication) as one of the followings:
[1] "primary study condition" (except acute treatment)
[2] corresponding medical history event (preferred term) that includes "migraine" (except acute treatment)

[3] corresponding adverse event (preferred term) that includes "migraine" (except acute treatment)

Note that all records in the prior therapy migraine medication CRF have the indication "primary study condition".

Previous migraine prevention therapy and migraine prevention therapy during SP III and SP IV (Section 5.5.9) will be reviewed by medical to exclude non-migraine prevention therapy before DBL.

Previous migraine acute treatment during SP II will be summarized by following categories (can be multiple classes):

- triptans,
- NSAIDs/aspirin,
- acetaminophen/paracetamol,
- ergots,
- anti-nausea
- Chinese medicine
- Others

Previous migraine acute treatment are migraine acute treatment used in during SP II. Migraine acute treatments will be identified either by eDiary or by the concomitant medication CRF with one of the following indications:
[1] "primary study condition" (except migraine prevention therapies)
[2] corresponding medical history event (preferred term) that includes "migraine" (except migraine prevention therapies)
[3] corresponding adverse event (preferred term) that includes "migraine" (except migraine prevention therapies)

Previous migraine acute treatment and migraine acute treatment during SP III and SP IV (Section 5.5.9) will be reviewed by medical to exclude non-acute treatment and to categorize them into the above definitions before DBL.

Regarding migraine acute treatment (and previous migraine acute treatment), combination medications (such as aspirin/acetaminophen/caffeine) will be counted in each medication category that applies (such as NSAIDs/aspirin and Acetaminophen/paracetamol).

5.5.9. Concomitant Therapy, Migraine Prevention Therapy, and Migraine Acute Treatment.

The proportion of patients who received concomitant medication will be summarized for ITT population for Study Period III and for the post-treatment population for Study Period IV separately. The concomitant therapy does not include migraine acute (abortive) treatments or migraine prevention therapy.

Concomitant therapies for study period III are those which started, stopped or continued in study period III. If medication started and stopped on the same day of injection, it will still be considered as concomitant medication for SP III. If medication started before the first day of injection but stopped on the same day of injection, then it will not be counted as concomitant medication for SP III.

Concomitant therapies for study period IV are those which either started, stopped or continued in Study Period IV. If medication started and stopped on the first day of SP IV, it will still be considered as concomitant medication for SP IV.

Treatment group comparisons will be done using the Fisher's exact test for Study Period III with ITT population. Descriptive statistics only will be presented for the treatment groups in Study Period IV with the post-treatment population.

Similar outputs for migraine prevention therapy will be created for SP III and SP IV. As mentioned in the previous section, the definition of the prevention therapy will be reviewed by medical before DBL.

Similar outputs for migraine acute treatment will be created for SP III and SP IV separately. The categorization is based on Section 5.5.8.

5.5.10. Efficacy Analyses

5.5.10.1. Primary Outcome and Methodology

The primary efficacy objective is to assess whether at least 1 dose of LY2951742 (120 or 240 mg/month) is superior to placebo in the prevention of migraine headache in patients with episodic migraine.

The primary analysis will evaluate the efficacy of LY2951742 (120, or 240 mg/month) compared with placebo on the overall mean change from baseline in the number of monthly migraine headache days during the 6-month treatment phase.

The primary analyses will be performed using a REML-based MMRM technique. The analysis will include the fixed categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of migraine headache days and baseline-by-month interaction.

An unstructured covariance structure will be used to model the within-patient errors. The Kenward-Roger (Kenward and Roger 1997) approximation will be used to estimate denominator degrees of freedom. If the model does not converge, the Fisher scoring algorithm will be implemented by specifying the SCORING option (SCORING=5) in SAS. If the model still fails to converge, the model will be fit using covariance matrices of the following order specified by a decreasing number of covariance parameters until convergence is met:

- Heterogeneous Toeplitz = toeph
- Heterogeneous First-order autoregressive = arh(1)
- Toeplitz = toep
- First-order autoregressive = ar(1)

Hence we fit the model by the following order:

[1] unstructured covariance with the default fitting,

[2] unstructured covariate with the Fisher scoring,

[3] toeph covariance with the default fitting,

[4] toeph covariance with the Fisher scoring

[5] arh(1) covariance with the default fitting,

[6] arh(1) covariance with the Fisher scoring

[7] toep covariance with the default fitting,

[8] toep covariance with the Fisher scoring

[9] ar(1) covariance with the default fitting,

[10] ar(1) covariance with the Fisher scoring

When the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle and Kenward 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is implemented by specifying the EMPIRICAL option in SAS®. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN (DDFM=BW) option in SAS®. If the model is still non-convergence, then baseline-by-month interaction may be excluded from the model.

The primary endpoint of this study for each LY2951742 dose arm compared with placebo will be estimated as the main effect of treatment from the MMRM analysis during the 6-month treatment phase. This provides the average treatment effect across 6 months of double-blind treatment phase. The repeated-measures analysis will include data from all 3 treatment groups. The Type I error rate for the study will be controlled at a 2-sided 0.05 level (equivalently, one-sided 0.025 level). For the multiplicity adjusted p-value calculation for the primary endpoint, the pairwise treatment effect comparisons of each dose of LY2951742 versus placebo will be conducted using the Step-down version of Dunnett' s procedure.

To implement the multiplicity adjustment, SAS® PROC GLIMMIX (with dist=normal option and residual option) will be used with the "adjust=dunnett stepdown" option. When the model is

fit with unstructured covariance, "adjust=dunnett stepdown ADJDFE=ROW" option will be used to adjust denominator degrees of freedom. The adjusted p-values will be reported for both LY arms (control arm is placebo).

The primary analysis will be also performed without multiplicity adjustment by SAS® PROC MIXED. This is mainly to show point estimators at each month and associated 95% confidence intervals.

The results of the statistical tests (by SAS® PROC MIXED) at each month in the double-blinded treatment phase from the primary analysis model will be used to assess the onset of effect for each LY2951742 dose arm compared with Placebo. In particular, if the primary efficacy analysis is statistically significant (with multiplicity adjustment), then the earliest month when statistical significance (without multiplicity adjustment) is observed and maintained for all the subsequent months during double-blinded treatment phase will be considered as the onset of effect.

The primary efficacy result (by SAS® PROC MIXED) will be plotted by each treatment arm (horizontal axis= month, vertical axis = change from baseline).

Effect size for change in migraine headache days (primary analysis) and number needed to treat for 50%, 75% and 100% response rate (key secondary analysis) will be created (time point=overall during 6 month double blind period) .

5.5.10.2. Sensitivity Analysis for Primary Outcome

Several types of sensitivity analyses are planned to assess the robustness of deviations from the assumptions of primary analysis including the target population, missing data assumption, and normality assumption and the influence of slight change in the definition of episodic migraine prevention.

Target population Assumption

Sensitivity analyses will be performed using different target population. They are implemented by repeating the primary analysis using PPS instead of ITT. Per protocol set excludes patients who hit criteria of important protocol deviation which would affect the primary efficacy analysis.

Missing Data Assumption

Sensitivity analyses will be performed to assess the robustness of the primary analysis conclusions to deviations from MAR assumption. The approach for these analyses is to vary the assumptions of missing data for the primary analysis in a systematic way. Basically, the method will be to predict the missing outcomes and then add values (Δ_{120},Δ_{240},Δ_P) to the predictions in the LY2951742 120 mg/month, LY2951742 240 mg/month, and placebo treatment groups respectively, consistent with the sensitivity approach suggested in Permutt (2015). This procedure will be repeated multiple times for different values of (Δ_{120},Δ_{240},Δ_P) using the following steps:

1) Predict the missing outcomes for each treatment via multiple imputation based on observed primary endpoint and baseline values. Such imputation will be carried out using a Markov Chain Monte Carlo method with a Jeffreys prior via SAS® PROC MI. Thirty (30) such imputations will be created.
2) Add the corresponding Δ value (i.e., Δ_{120},Δ_{240}, or Δ_P) to the imputed values based on the patient treatment group.
3) Conduct the primary analysis separately for each of the 30 imputations.
4) Combine the results of these analyses using Rubin's combining rules, as implemented in SAS® PROC MI ANALYZE.

The above steps will be repeated multiple times for different values of (Δ_{120},Δ_{240},Δ_P) with Δ_P ranging from (0, twice the absolute value of the mean value seen for placebo in the primary analysis) and both Δ_{120} and Δ_{240} ranging from (Δ_P, Δ_P + absolute value of the biggest mean treatment difference seen within the primary analysis). For example, if the overall mean change from baseline for placebo is -3.6 and the maximum overall treatment difference is -1.5, then Δ_P would range from (0,7.2) and Δ_{120} and Δ_{240} would range from (Δ_P, Δ_P+ 1.5).

Normality Assumption

To assess the robustness of the MMRM results to deviations from normality assumption, a sensitivity analysis for the raw number of migraine headache days (the total number of migraine headache days for each interval without normalization to 30-day period) will be conducted with a repeated measures negative binomial regression analysis fitted with SAS PROC GLIMMIX. The model will include treatment, month, and treatment-by-month interaction, as well as the continuous fixed covariates of baseline number of monthly migraine headache days and baseline-by-month interaction, log (number of compliant calendar days within each month/30) as the offset in the model. In case of non-convergence, baseline-by-month interaction may be excluded from the model.

Definition of Episodic Migraine Headache

This sensitivity analysis is to assess the robustness of the primary results to the deviation of minor change in the definition of migraine (See Criteria C. below). It is implemented by repeating the primary analysis using the number of monthly migraine headache days derived based on the following definition of migraine, which aligns with migraine headache days definition in chronic migraine, but is considered relevant for the episodic population, as well.

> A headache, with or without aura, of ≥30 minute's duration with both of the following required features (Criteria A and Criteria B):
> Criteria A. At least 2 of the following headache characteristics:
> - Unilateral location
> - Pulsatile quality
> - Moderate or severe pain intensity
> - Aggravation by or causing avoidance of routine physical activity
>
> AND
> Criteria B. During headache at least one of the following:

- Nausea and/or vomiting
- Photophobia and phonophobia

OR

Criteria C. Patient takes a triptan or ergot derivative.

In other words, if [Criteria A and Criteria B] or [Criteria C] is satisfied, then it is considered as "MHD with Criteria C".

ANCOVA

Using LOCF imputation, the primary analysis is conducted with ANCOVA (without multiplicity adjustment) described in Section 5.5.1.1.

Baseline definition by IWRS based eligibility date

Instead of using ePRO eligibility date, the one by IWRS will be used for the primary analysis without multiplicity adjustment (by PROC MIXED).

5.5.10.3. Secondary and Exploratory Efficacy Analyses

Table CGAN. 5.5 summarizes planned efficacy analyses for Study Period III, Study Period III/IV, and Study Period IV. All response rates are derived from migraine headache days unless otherwise specified. There will be no multiplicity adjustment for statistical test except for the primary efficacy analysis.

If analysis results would be considered less informative, then such results may not be provided in CSR. For example, the change from baseline analysis for number of migraine headache days with triptan use, if baseline values (see Section 5.5.4) are less than 1 day for at least one of the arms, then these analysis may not be provided in CSR because the improvement (change from baseline) is difficult to evaluate.

Continuous Efficacy Measures

For the continuous efficacy measures, the change from baseline to each post-baseline period will be estimated for each treatment from repeated measures analyses as described for analysis for primary outcome, using PROC MIXED.

For the continuous secondary efficacy measures where the objective is to assess overall mean change during 6-month treatment phase, the endpoint for comparing LY2951742 with placebo will be estimated as the main effect of treatment from the MMRM analysis across Months 1-6.

Binary Efficacy Measures

For the repeated binary efficacy measures such as responder indicators based on the number of migraine headache days, the visitwise binary responder indicators will be analyzed using a categorical, pseudo-likelihood-based repeated measures analysis. This analysis will be implemented using the GLIMMIX procedure in SAS to compare treatments and include the

fixed, categorical effects of treatment, month, and treatment-by-month interaction, as well as the continuous, fixed covariate of baseline value.

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

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

- Heterogeneous Toeplitz = toeph
- Heterogeneous First-order autoregressive = arh(1)
- Toeplitz = toep
- First-order autoregressive = ar(1)

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

For models where the unstructured covariance matrix is not utilized, the sandwich estimator (Diggle et al. 1994) will be used to estimate the standard errors of the fixed effects parameters. The sandwich estimator is utilized by the EMPIRICAL option in SAS. When the sandwich estimator is utilized, the Kenward-Roger approximation for denominator degrees of freedom cannot be used. Instead, the denominator degrees of freedom will be partitioned into between-subject and within-subject portions by the DDFM=BETWITHIN option in SAS.

For the repeated binary secondary efficacy measures where the objective is to assess the proportion of patients with X% response during the 6-month double-blind treatment phase, the endpoint for comparing LY2951742 with placebo will be estimated as the main effect of treatment from the categorical MMRM analysis across Months 1-6.

For visitwise indicators of 50% responders, the results of the statistical tests at each month in the double-blinded treatment phase from categorical MMRM analysis (PROC GLIMMIX) will be used to assess the onset of 50% sustained response for LY2951742 compared to Placebo. In particular, if the key secondary measure of 50% response rate is statistically significant, then the earliest month where the statistical significance is observed and maintained for all the subsequent months during double-blinded treatment phase will be considered as the onset of 50% sustained response.

For non-repeated binary measures, such as 50% response sustained for three consecutive months until patient's endpoint in 6-month treatment phase and 50% response sustained from month 1 to

month 6, a logistic regression analysis with covariates of treatment and baseline will be conducted.

Measures Conditional on the Post-baseline Number of Migraine Headache Days >0

Some measures are conditional on the number of migraine headache days >0 such as:

- Mean severity of remaining migraine on migraine headache days
- Proportion of migraine headache days with abortive (acute) medication use
- Average number of classes of abortive medications used per migraine headache day

They will be modelled individually using the MMRM model, assuming data are missing during months without migraine headache.

Analyses for Number of Weekly Migraine Headache Days in Month 1

The number of weekly migraine headache days in Month 1 can be considered as ordinal data with possible values of 0, 1, 2, 3, 4, etc. (Note: week 4 may have more than 7 migraine headache days because of the definition. If duration of Visit 3 to Visit 5 is 31 days, then duration of week 4 is 10 days with day 22, day 23,…, day31) It will be analyzed using an ordinal repeated measures model implemented using the GLIMMIX procedure in SAS. In this model, a proportional odds model with cumulative logit link will be used, and a random intercept will be applied to the observations for each patient to account for repeated measures. The model will include the fixed, categorical effects of treatment, week, and treatment-by-week interaction, as well as the continuous, fixed covariate of baseline number of migraine headache days (/month) and baseline number of migraine headache days by week interaction. Log (number of compliant calendar days within each week/7) will be used as the offset in the model.

Time to Event Measures

For the following time to event measures, a Kaplan-Meier curve of the time to event and treatment group comparison using log-rank test stratified by baseline MHD frequency category (<8 vs >=8 migraine headache days per 30-day period) will be provided.

- Time to first 50% response in double-blind treatment phase
- Time to first loss of 50% response in post-treatment phase (SP III completer only)
- Time to initiation of preventative treatment for migraine or probable migraine in post-treatment phase (SP III completer only)

Distribution of Response Rates

Overall x% response rate during the double-blind treatment phase will be estimated for X=0, 5, 10,…, 95, and 100, using GLIMMIX model as described earlier in this section. These estimated response rates will be plotted and points within each treatment arm will be connected to show a

curve of response rates. No statistical comparisons will be conducted among different treatment arms.

Analysis for PGI-S

Change from baseline in PGI-S scores will be analyzed.

PGI-S responder analysis will be conducted.

Analysis for PGI-I

The PGI-I raw value will be analyzed with a mixed model repeated measures analysis with PGI-S baseline score.

PGI-I responder analysis (Weighted Mean of PGI-I Responder analysis) will be analyzed. 95% confidence interval will be generated using nonparametric Monte Carlo bootstrap.

Table CGAN. 5.5 Primary, Secondary and Exploratory Efficacy Variables and Analysis Methods

Efficacy Variables	Analysis in SP III	Analysis in SP III/IV	Analysis in SP IV only
Number of MHD	MMRM/ANCOVA	MMRM	NA
Number of MHD with Criteria C	MMRM	NA	NA
Number of migraine headache hours	MMRM	NA	NA
Number of migraine attacks	MMRM	NA	NA
Number of days with acute medication use	MMRM	NA	NA
Number of MHD with acute medication use	MMRM	MMRM	NA
Proportion of MHD with acute medication use	MMRM	NA	NA
Number of headache days	MMRM	NA	NA
Number of moderate-severe headache days	MMRM	NA	NA
Number of headache hours	MMRM	NA	NA
Number of ICHD MHD	MMRM	NA	NA
Mean severity of migraine headache	MMRM	NA	NA
Number of MHD with nausea and/or vomiting	MMRM	NA	NA
Number of MHD with photophobia and	MMRM	NA	NA

phonophobia			
Number of MHD with aura	MMRM	NA	NA
Number of MHD prodrome symptoms other than aura	MMRM	NA	NA
Number of non-MHD with aura	MMRM	NA	NA
Proportion of Aura within migraine attack	MMRM	NA	NA
Number of classes of acute medication use	MMRM	NA	NA
Number of classes of acute medications used on MHD	MMRM	NA	NA
Average number of classes of acute medication use	MMRM	NA	NA
Average number of classes of acute medication use on MHD	MMRM	NA	NA
Number of MHD with menstrual period	MMRM	NA	NA
Number of days with triptans use	MMRM	NA	NA
Number of MHD with triptans use	MMRM	NA	NA
Number of days with NSAIDS/Aspirin use	MMRM	NA	NA
Number of MHD with NSAIDS/Aspirin use	MMRM	NA	NA
Number of days with Acetaminophen/paracetamol use	MMRM	NA	NA
Number of MHD with Acetaminophen/paracetamol use	MMRM	NA	NA
Number of days with Ergots use	MMRM	NA	NA
Number of MHD with Ergots use	MMRM	NA	NA
Number of days with Anti-nausea use	MMRM	NA	NA
Number of MHD with Anti-nausea use	MMRM	NA	NA
Number of days with Multi-Class acute medication use	MMRM	NA	NA
Number of MHD with Multi-Class acute medication use	MMRM	NA	NA
Number of days with acute medication use on non-headache days	MMRM	NA	NA
PGI-S	MMRM	MMRM	NA

PGI-I (adjusting for PGI-S)	MMRM	NA	NA
MSQ Total	MMRM	MMRM	NA
MSQ Role Function-Restrictive domain	MMRM	MMRM	NA
MSQ Role Function-Preventive domain	MMRM	MMRM	NA
MSQ Emotional Function domain	MMRM	MMRM	NA
MIDAS Total (sum of item 1, 2, 3, 4, and 5)	MMRM	MMRM	NA
MIDAS individual items (item 1, 2, 3, 4, 5, A, and B)	MMRM	NA	NA
HCRU Summary	Descriptive	NA	Descriptive
HCRU Migraine related events/100-patients-year	Descriptive	NA	Descriptive
HCRU Employment status	Descriptive	NA	Descriptive
Number of weekly MHD in month 1	GLIMMIX	NA	NA
X% response rate (X=50, 75, or 100)	GLIMMIX	GLIMMIX	NA
30% response rate	GLIMMIX	NA	NA
Distribution of response rate in SP III	GLIMMIX	NA	NA
Time to first 50% response in SPIII	KM/log-rank test	NA	NA
Maintenance of 50% response for the last 3 months or 6 months	Logistic regression	NA	NA
Time from the end of SP III to no longer meeting 50% response criterion	NA	NA	KM/log-rank test
Time from the end of SP III to start use of preventative treatment for migraine	NA	NA	KM/log-rank test
PGI-S responder (2>= improvement)	GLIMMIX	NA	NA
PGI-I responder (Top 2 categories)	Weighted mean	NA	NA
MIDAS 50% responder at month 6	GLIMMIX	NA	NA
MSQ Role Function-Restrictive responder (>=25)	Logistic regression	NA	NA
PSMQ-M summary (with positive response)	Logistic regression	NA	NA

Abbreviations: ANCOVA = analysis of covariance; GLIMMIX = Generalized linear mixed model (for binary variables); HCRU = HealthCare Resource Utilization; ICHD = International Classification of Headache Disorders; KM/log-rank test = Kaplan Meier curve and stratified log-rank test; MHD=migraine headache days; MIDAS = Migraine Disability Assessment; MMRM = Mixed models repeated measures; MSQ = Migraine-Specific Quality; NA = not applicable. PGI-I = Patient Global Impression-Improvement; PGI-S = Patient Global Impression-Severity; PSMQ-M = Patient Satisfaction with Medication Questionnaire-Modified; SP = Study Period;

5.5.11. Quality-of-Life (QoL) Analyses

5.5.11.1. MSQ

The mean change from baseline to each post-baseline visit for Study Period III and Study Period III/IV for MSQ total score and 3 domain scores will be evaluated using MMRM as described in Section 5.5.10.1. The endpoint for comparing LY2951742 with placebo will be estimated using a CONSTRAST statement in PROC MIXED as the average across Months 4-6 and overall (Month 1- Month 6).

MSQ Role Function-Restrictive domain responders (based on the average score of change from baseline at month 4, 5, and 6 $\geq$25) in SP III will be analyzed using logistic regression.

5.5.11.2. MIDAS

MMRM described in Section 5.5.10.1 will be used for the following analysis:

- For SP III, the mean change from baseline to each post-baseline visit (month 3, month 6) and overall will be analyzed (the response variables are total score, each item 1, 2, 3, 4, 5, A, and B).
- For SP III/IV combined, the mean change from baseline to each visit (month 3, month 6, month 10) will be analyzed (the response variable is total score).

MIDAS responders ($\geq$50% improvement in MIDAS total score) at each evaluated month, and overall in SP III will be analyzed using GLIMMIX. Here overall is taken from the main effect of the model.

5.5.11.3. HCRU

For HCRU, descriptive summary of Question 1-3 will be created. Analysis period is SP I/II/III/IV combined. It includes baseline (over the last 6 months period from Visit 3), SP III (6 months period), and SP IV (4 months period) with ITT population. In particular, for each period, the summary of following will be created:

- number of emergency room visits (Q1)
- number of emergency room visits related to migraine (Q1)
- number of overnight hospitalization (unit=incidence) (Q2)
- number of overnight hospitalization related to migraine (unit=incidence) (Q2)
- number of overnight hospitalization (unit=day) (Q2)
- number of overnight hospitalization related to migraine(unit=day) (Q2)
- number of healthcare professional visits (Q3)
- number of healthcare professional visits related to migraine (Q3)

Summary of HCRU related to migraine will be created. The unit is per 100 patient years. 100 patient year is defined as

100*(sum of all events)/ (number of total months with patient data/12).

Descriptive summary of working status (Question 4) will be created for each month: Analysis period is SP III/IV combined. It includes month 0 to month 6, month 8, and month 10 with ITT population.

5.5.11.4. PSMQ-M

Summary of each item, as well as positive response defined in Section 5.4.3.4 will be created using descriptive statistics for each month (month 1 and month 6) in SP III.

For positive responses at Month 6, logistic model will be used for treatment comparison.

5.5.12. Safety Analyses

The safety analyses will be conducted for Study Period III, Study Period IV, and/or Study Period III and IV combined.

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

- Adverse events
  - hypersensitivity events
  - injection sites
  - upper respiratory tract infections

- Suicide-related thoughts and behaviors
- Vital signs and weight
- Laboratory measurements
- ECGs
- Antibodies (ADA and NAb)

The baseline and post-baseline for all safety measures are described in Table CGAN. 5.4, unless specified otherwise.

For laboratory, vital, weight, ECG and ADA, categorical and/or continuous analysis will be conducted. Detail analysis are specified in the following sections.

5.5.12.1. Categorical Safety Variables

Unless specified otherwise, the categorical safety analyses will include both scheduled and unscheduled visits. Unless otherwise specified, categorical safety analyses will only be conducted for Study Period III and Study Period IV separately.

Comparisons between treatment groups for all categorical safety measures will be made using the Fisher's exact test for Study Period III with the safety population.

Descriptive statistics only will be presented for the treatment groups in Study Period IV with the post-treatment population.

5.5.12.1.1. Adverse Events

Treatment-emergent adverse events are defined as the reported AEs that first occurred or worsened during the post-baseline phase compared with the baseline phase. Pre-existing condition that is still ongoing at Visit 1 should be evaluated as baseline values. For each TEAE, the severity level of the event (mild, moderate, or severe) will be determined by patient or physician opinion. The MedDRA Lowest Level Term (LLT) will be used in the treatment emergent computation. For each LLT, the maximum severity at baseline will be used as the baseline severity. If the maximum severity during post-baseline is greater than the maximum baseline severity, the event is considered to be treatment emergent for the specific post-baseline period. For each patient and TEAE, the maximum severity for the MedDRA level being displayed (PT, High Level Term, or SOC) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level.

Follow-up emergent adverse events (post-treatment emergent adverse events) are defined similarly. It is an event that first occurred or worsened during the follow-up period (Study Period IV) when compared to the baseline (SP I, SP II, and SP III). Pre-existing condition that is still ongoing at Visit 1 should be evaluated as baseline values.

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

Following summary will be created:

- Overview of AE (SP III)
- TEAEs (SP III)
  - By PT by decreasing frequency
  - By PT by decreasing frequency with an incidence in either galcanezumab treatment group ≥1.5% and greater than placebo.
  - By SOC/PT
  - By maximum severity/PT
- FEAEs (SP IV)
  - By PT by decreasing frequency
  - By SOC/PT
  - By maximum severity/PT
- TEAEs by considered to be related to investigational product by investigator (SP III)
- Treatment Emergent Adverse Events that started on Treatment phase and Continuing in Post-Treatment Phase (SP III, SP IV combined)
- SAEs (SP III, SP IV separately)
- AEs leading to discontinuation (SP III, SP IV separately)

Listing of Subjects with TEAE or FEAE (SP III, SP IV combined) will be created.

Listing of Adverse Events Leading to Discontinuation and Serious Adverse Events (SP I, SP II, SP III, SP IV combined) will be created.

5.5.12.1.1.1. Hypersensitivity events

Potential hypersensitivity events (immediate and no immediate) will be identified from a review of preferred terms generated from the following queries:

- Broad and narrow terms in the Anaphylactic reaction SMQ (20000021)
- Broad and narrow terms in the Angioedema SMQ (20000024)
- Broad and narrow terms in the Hypersensitivity SMQ(20000214)

Summary for the potential hypersensitivity events (SP III, SP IV separately) will be created. These analyses will be medically reviewed to determine if the terms identified represent actual hypersensitivity events before unblinding. Only those that are judged medically to be hypersensitivity events will be included in the tables of "hypersensitivity events".

The number and percentage of patients with TEAEs (SP III, SP IV separately) and AEs resulting in study drug discontinuation (SP III) will be summarized by treatment groups using MedDRA PT nested within the SMQ. Events will be ordered by decreasing frequency within the SMQ.

The number and percentage of patients with treatment-emergent hypersensitivity events by maximum severity (SP III) will be summarized by treatment groups using MedDRA PT.

The number and percentage of patients with TEAEs hypersensitivity events by timing (SP III) will be summarized using MedDRA PT nested within the SMQ. Events will be ordered by decreasing frequency. Note the timing of the hypersensitivity events is collected through eCRF and categorized into the following categories:

- During drug administration
- Within 30 minutes of end of study drug administration
- 30 minutes and up to 6 hours from end of study drug administration
- 6 hours and up to 24 hours from end of study drug administration
- 24 hours and up to 14 days from end of study drug administration
- Greater than 14 days from end of study drug administration

If these information was not collected, then such data will be excluded from the timing analysis.

The relationship between the development of treatment-emergent hypersensitivity events and TEAEs related to injection sites (SP III) will be summarized.

A listing of Subjects with Treatment-Emergent or Post-Treatment Emergent Potential Hypersensitivity Events will be created.

5.5.12.1.1.2. Adverse Events Related to Injection and Site

Adverse events related to injection sites will be defined using terms from the MedDRA High Level Term "Injection Site Reactions".

The number and percentage of patients with TEAEs related to injection sites (SP III) and AEs related to injection sites resulting in study drug discontinuation (SP III) will be summarized using MedDRA PT. Events will be ordered by decreasing frequency within High Level Term.

The number and percentage of patients with TEAEs related to injection sites by maximum severity (SP III) will be summarized by treatment groups using MedDRA PT. For each patient and AEs related to injection sites, the maximum severity for the MedDRA level being displayed (PT) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level.

The number and percentage of patients with TEAEs of injection sites by timing (SP III) will be summarized using MedDRA preferred terms ordered by decreasing frequency. Note the timing of injection site reactions is collected through eCRF and categorized as follows:

- Occurs during study drug administration
- Occurs within minutes (<60 minutes) of study drug administration
- Occurs from 1 up to 6 hours of study drug administration
- Occurs from >6 hours through 14 days from study drug administration, which will be split into two categories: on the same day of injection and after the day of injection
- Occurs >14 days of study drug administration

If these information was not collected, then such data will be excluded from the timing analysis.

Listing of Subjects with Treatment-Emergent Adverse Events Related to Injection Sites will be created.

Summary of Injection Site Reaction by Max Severity, by Anatomical Location (Abdomen, Arm, Buttock, and Thigh) will be created.

Figure of duration of Injection Site related Adverse Events for each PT will be created

5.5.12.1.1.3. Upper Respiratory Tract Infections

Upper respiratory tract infections will be defined using all the PTs from the two high level terms of "upper respiratory tract infections" and "upper respiratory tract infections NEC" as defined in MedDRA.

The number and percentage of patients with TEAEs of Upper respiratory tract infections (SP III and SP IV separately) and resulting in study drug discontinuation (SP III) will be summarized by treatment group using MedDRA PTs. Events will be ordered by decreasing frequency.

The number and percentage of patients with TEAEs of upper respiratory tract infections by maximum severity (SP III) will be summarized by treatment groups using MedDRA PT. For each patient and upper respiratory tract infection event, the maximum severity for the MedDRA level being displayed (PT) is the maximum post-baseline severity observed from all associated LLTs mapping to that MedDRA level.

Listing of Subjects with Treatment-Emergent or Post-Treatment Emergent Upper Respiratory tract infection (SP III, SP IV combined) will be created.

5.5.12.1.2. Suicide-Related Thoughts and Behaviors

Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent based on the Columbia-Suicide Severity Rating Scale (C-SSRS), will be summarized by treatment (SP III,

SP IV separately). In particular, for each of the following events, the number and percent of patients with the event will be enumerated by treatment: completed suicide, nonfatal suicide attempt, interrupted attempt, aborted attempt, preparatory acts or behavior, active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods (no plan) without intent to act, nonspecific active suicidal thoughts, wish to be dead, and self-injurious behavior without suicidal intent.

In addition, the number and percent of patients who experienced at least one of various composite measures during Study Period III and Study Period IV separately will be presented and compared. Composite measures include followings:

- Suicidal behavior (completed suicide, non-fatal suicidal attempts, interrupted attempts, aborted attempts, and preparatory acts or behavior),
- Suicidal ideation (active suicidal ideation with specific plan and intent, active suicidal ideation with some intent to act without specific plan, active suicidal ideation with any methods [no plan] without intent to act, non-specific active suicidal thoughts, and wish to be dead)
- Suicidal ideation or behavior.

The number and percent of patients who experienced at least one of various comparative measures during treatment will be presented and compared for study period III and summarized for SP IV. Comparative measures include followings:

- TE suicidal ideation (1-5) compared to recent history,
- TE suicidal ideation (1-5) compared to all prior history,
- TE serious suicidal ideation (0-3 to 4-5) compared to recent history,
- TE serious suicidal ideation (0-3 to 4-5) compared to all prior history,
- Emergence of serious suicidal ideation (0 to 4-5) compared to recent history
- Emergence of serious suicidal ideation (0 to 4-5) compared to all prior history
- Improvement in suicidal ideation at endpoint compared to baseline,
- Emergence of suicidal behavior (6-10) compared to all prior history.

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

Category 1 – Wish to be Dead
Category 2 – Non-specific Active Suicidal Thoughts
Category 3 – Active Suicidal Ideation with Any Methods (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.

The following outcome is a numerical score derived from the C-SSRS categories. The score is created at each assessment for each patient and is used for determining treatment emergence.

- Suicidal Ideation Score: The maximum suicidal ideation category (1-5 on the C-SSRS) present at the assessment. Assign a score of 0 if no ideation is present.

For Study Period III and SP IV, comparative endpoints of interest are defined below. "Treatment emergence" is used for outcomes that include events that first emerge or worsen. "Emergence" is used for outcomes that include events that first emerge.

- Treatment emergent suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score during treatment (Visits 3.01 to 12 for SP III; Visits 12.01 to 14 for SP IV) from the maximum suicidal ideation category during the screening and lead-in periods (C-SSRS scales taken at Visits 1 to 3 excluding "lifetime" for SP III; C-SSRS scales taken at Visits 1 to 12 excluding "lifetime" for SP IV). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale
- Treatment emergent suicidal ideation compared to all prior history:

  The same definition above except the baseline includes "lifetime" scores.

- Treatment emergent serious suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment (Visits 3.01 to 12 for SP III; Visits 12.01 to 14 for SP IV) from not having serious suicidal ideation (scores of 0-3) during the screening and lead-in periods (C-SSRS scales taken at Visits 1-3 excluding "lifetime" for SP III; C-SSRS scales taken at Visits 1 to 12 excluding "lifetime" for SP IV). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.

- Treatment emergent serious suicidal ideation compared to all prior history:

  The same definition above except the baseline includes "lifetime" scores.

- Emergence of serious suicidal ideation compared to recent history:
  An increase in the maximum suicidal ideation score to 4 or 5 on the C-SSRS during treatment (Visits 3.01 to 12 for SP III; Visits 12.01 to 14 for SP IV) from no suicidal ideation (scores of 0) during the screening and lead-in periods (C-SSRS scales taken at Visits 1 to 3 excluding "lifetime" for SP III; C-SSRS scales taken at Visits 1 to 12 excluding "lifetime" for SP IV). Recent history excludes "lifetime" scores from the Baseline C-SSRS scale or Baseline/Screening C-SSRS scale.
- Improvement in suicidal ideation at endpoint compared to baseline:
  A decrease in suicidal ideation score at endpoint (the last measurement during treatment; Visits 3.01 to 12 for SP III; the last measurement during open-label phase Visits 12.01 to 14 for SP IV) from the baseline measurement (the measurement taken just prior to treatment Visit 3 for SP III; the last non-missing measure during Visits 3.01 to 12 for SP IV).
- Emergence of suicidal behavior compared to all prior history:
  The occurrence of suicidal behavior (Categories 6-10) during treatment (Visits 3.01-12 for SP III; Visits 12.01 to 14 for SP IV) from not having suicidal behavior (Categories 6-10) prior to treatment (Visits 1-3 including "lifetime" for SP III; C-SSRS scales taken at Visits 1 to 12 including "lifetime" for SP IV).

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

Listing of Subjects with Suicidal Ideation, Behavior, or Self-injurious Behavior at Any Time Post-Baseline will be created.

5.5.12.1.3. Vital Signs and Weight

Vital signs collected during the study include systolic and diastolic blood pressure, pulse, and temperature. Blood pressure and pulse will be measured in triplicate, in the sitting position, and should be measured prior to blood draws. The three sitting blood pressure measurements and three pulse values will be averaged and used as the value for that visit. If the measurements are less than three, the average will be calculated by existing values.

The number and percent of patients meeting criteria for treatment-emergent abnormalities in vital signs and weight at any time during study will be summarized (SP III and SP IV separately). Treatment group comparisons will be performed using the Fisher's exact test for SP III. Table CGAN. 5.6 displays the criteria used to define treatment emergent changes in vital signs and weight. The last column of the table displays the patient populations defined by baseline categories, the treatment emergent categorical changes will be analyzed for each of those patient populations for SP III. The criteria generally consist of two parts, an absolute threshold and a change from baseline amount. The baseline and post-baseline definitions for vital signs analyses are in Table CGAN. 5.4.

Listing of Subjects with Categorical Changes of Interest in Vital Signs and Weight at any time during SP III and SP IV will be created.

Table CGAN. 5.6. Criteria for Treatment Emergent 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
	Sustained Elevation	≥140 and increase ≥20 at 2 consecutive visits	All patients; <140; ≥140
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
	Sustained Elevation	≥90 and increase ≥10 at 2 consecutive visits	All patients; <90; ≥90
Systolic BP or Diastolic BP (mm Hg) (sitting)	Sustained Elevation	Meeting criteria for systolic BP for 2 consecutive visits or meeting criteria for diastolic BP for 2 consecutive visits or both	All Patients
Pulse (bpm) (sitting)	Low	<50 and decrease ≥15	All patients; ≥50; <50
	High	>100 and increase ≥15	All patients; ≤100; >100
	Sustained Elevation	>100 and increase ≥15 at 2 consecutive visits	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.

Note: consecutive visits include unscheduled visits.

5.5.12.1.4. Electrocardiogram Intervals and Heart Rate

Analyses of corrected QT (QTc) interval will be calculated using two correction formulas. The QTcF (msec) will be calculated with Fridericia's formula as $QT/RR^{1/3}$. The Large Clinical Trial Population Based QT Correction (QTcLCTPB) (msec) will be calculated with the formula as $QT/RR^{0.413}$. For the QTc calculations, the unit for QT is milliseconds and the unit for RR is seconds. For patients with QRS ≥120 milliseconds at any time during the study (including before randomization and SP IV), the QTc interval (e.g., QTcF and QTcLCTPB) for that patients will be excluded from the analyses (change from baseline to LOCF endpoint analysis, categorical analysis).

A listing of Subjects with post-baseline emergent ECG findings (SP III, SP IV combined) will be created which ignore QTc related abnormality for patients with QRS ≥120 milliseconds but include the other abnormalities such as heart rate, as well as QRS.

A listing of ECG data for patients with QRS ≥120 milliseconds at any time during the study will be provided. (SP I, SP III and SP IV combined)

The number and percent of patients meeting criteria for treatment emergent abnormalities in ECG intervals (PR, QRS, QTcF, and QTcLCTPB) and heart rate at any time during study will be summarized (SP III, SP IV separately) Treatment group comparisons will be performed using the Fisher's exact test for SP III.

Table CGAN. 5.7 displays the criteria for treatment emergent changes in ECG intervals, such as heart rate and QTcLCTPB. For QTcLCTPB, the treatment emergent low and high criteria are listed by gender and age range, based on Lilly reference ranges.

- For Treatment emergent low analyses: Patients with all normal or high values at baseline (no low values) and at least one post-baseline result will be included.
- For Treatment emergent high analyses: Patients with all normal or low values at baseline (no high values) and at least one post-baseline result will be included.
- For Treatment emergent increase analyses: Patients with a baseline and at least one post-baseline result will be included.

The baseline and post-baseline values are summarized in Table CGAN. 5.4.

Table CGAN. 5.7 Criteria for Treatment Emergent Changes in ECG Intervals and Heart Rate

Parameter	Direction	Criteria	
Heart Rate (bpm)	Low	<50 and decrease ≥15	
	High	>100 and increase ≥15	
PR Interval (msec)	Low	<120	
	High	≥220	
QRS Interval (msec)	Low	<60	
	High	≥120	
QTcF (msec)	Low	Males: <330	Females: <340
	High	Males: >450	Females: >470
	PCS High	>500msec	
	Increase	Increase >30 msec	
		Increase >60 msec	
		Increase >75 msec	
QTcLCTPB (msec)	Low	Male (All ages): <330;	Female (All ages): <340
	High	Male Age (yrs): criteria <18: >444 18-25: >449 26-35: >438 36-45: >446 46-55: >452 56-65: >448 >65: >460	Female Age (yrs): criteria <18: >445 18-25: >455 26-35: >455 36-45: >459 46-55: >464 56-65: >469 >65: >465
	PCS High	>500 msec	
	Increase	Increase >30 msec	
		Increase >60 msec	
		Increase >75 msec	

Abbreviations: msec = millisecond; PCS = Potentially Clinically Significant; QTcF= The Fridericia's corrected QT interval; QTcLCTPB = The Large Clinical Trial Population Based QT Correction; yrs = years.

In addition, summary of qualitative ECG abnormalities (SP III with Fisher's exact test and SP IV without test) will be conducted which will include summaries of 11 ECG categories (Axis, Rhythm, Conduction, Ischemia, Infarction, Injury, Morphology, U-waves, T-waves, ST Segment, and Other Abnormalities) of qualitative findings at any time post-baseline for two population:

[1] Subjects who are baseline normal for a category,

[2] Subjects who are baseline normal for all of 11 categories.

Note that the output [1] contains overall interpretation result.

For SPIII and SP IV summaries, the baseline qualitative ECG status is defined as the status at last available qualitative ECG assessment during the baseline period (assessment day <=Visit 3 for SP III, and assessment day <=Visit 12 for SP IV). A category is a collection of possible descriptions (findings) of one qualitative aspect of an ECG. A category name is the name of the qualitative aspect of the ECG (for example, Rhythm, Conduction, Morphology, Ischemia, and so forth). A finding is 1 of the possible specific descriptions (for example, Sinus Bradycardia, Acute Septal Infarction) within a category.

Listing of Abnormal Qualitative ECG by Finding Category will be created (SP III, SP IV combined)

5.5.12.1.5. Laboratory Tests

The incidence rates of patients with treatment emergent abnormal, high, or low laboratory values based on Covance reference ranges at any time post-baseline will be assessed using the Fisher's exact test for each laboratory test for SP III and no tests for SP IV.

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

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

The incidence of patients with the following elevations in hepatic laboratory tests at any time post-baseline will also be summarized and compared between treatment groups using the Fisher's exact test for SP III and no tests for SP IV.

- 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 nonmissing maximum baseline value is less than or equal to 1 × ULN for ALT, AST, ALP, and TBIL.
- Patients whose nonmissing 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 nonmissing 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. (SP III, SP IV combined)

A listing of Subjects with abnormal Hepatic Laboratory Results will be created. (SP III, SP IV combined)

5.5.12.1.6. Immunogenicity

To evaluate the changes in immunogenicity data of

- Anti-LY2951742 Antibody (hereafter "Anti-Drug Antibody (ADA),")
- Neutralizing ADA (hereafter "Neutralizing Antibody (NAb)") after treatment,

the statistical analyses (Fisher's exact test) are planned for comparison between treatment groups.

The summary (baseline=Visit 3) will be created for

1. SP III (safety population)
2. SP III (ADA follow-up cohort)
3. SP III and SP IV combined (ADA follow-up cohort)

Analysis of each period include:

- The incidence of "ADA positive (%)" and "ADA positive and NAb Positive (%)" during baseline (Visit 3).

- The incidence of treatment emergent ADA (TE ADA) between treatment groups. The baseline and post-baseline definitions for each study period is shown in Table CGAN. 5.4. Treatment emergent ADA will be defined as any of the following:
    - A negative baseline result and a positive post-baseline ADA result with a titer ≥20. This is also called treatment-induced ADA.
    - A positive baseline result and a positive post-baseline ADA result with a ≥4-fold increase in titers (for example, baseline titer of 10 increasing to ≥40 post-baseline). This is called treatment-boosted ADA.
- The incidence of TE-ADA and NAb Positive combined.

Note that TE-ADA can happen at multiple visits during SP III (or SP III and SP IV combined) because the judgement is solely based on comparison between the particular visit and the baseline (Visit 3) (i.e., listings may contain multiple TE-ADA time points, although one TE-ADA point is enough to be considered being TE-ADA subject with that TE-ADA.)

The following will also be created:

- Listing of subjects with TE-ADA at any time during study (SP III and SP IV combined), NAb Status will also be displayed.
- Listing of subjects with ADA detected at any time during study (SP III and SP IV combined) excluding subjects with TE-ADA.
- Listing of subjects with TEAEs of hypersensitivity reactions or injection site reactions or ADA present at any time (SP III, SP IV).

5.5.12.2. Continuous Safety Measures

Analyses of continuous safety data will be conducted on safety patients who have a baseline and at least one post-baseline observation for each analysis period (SP III, SP IV, SPIII and SP IV combined).

When mixed model repeated measures analysis is used, values from unscheduled visits will be ignored and only value collected at scheduled visit will be used.

For the following continuous safety measures, changes from last baseline value to LOCF will be assessed using an ANCOVA model as described in Section 5.5.1.1 with the fixed categorical effects of treatment, baseline value as the covariate:

- laboratory for SP III
- laboratory for SP IV

- weight for SP III
- ECG for SP III
- ECG for SP IV

If repeat laboratory values, weight or ECG exist at the same scheduled visit, only the last nonmissing value at a visit (selected by using the variable with highest lab sequence ID) will be used in the ANCOVA analysis for mean change from the last baseline value to LOCF endpoint.

For the following safety measures, the mean change from baseline will be analyzed using a mixed model repeated measures analysis. The analysis will include the fixed categorical effects of treatment, month and treatment-by-month interaction, as well as the continuous fixed covariates of baseline value and baseline-by-month interaction:

- vitals (SBP, DBP, Pulse) for SP III
- vitals (SBP, DBP, Pulse) for SP III and SP IV combined (safety population)
- weight for SP III and SP IV combined (safety population)
- temperature for SP III
- temperature for SP III and SP IV combined (safety population)

5.5.13. Subgroup Analyses

Subgroup analyses will be performed for primary efficacy measure (change from baseline in the number of monthly migraine headache days) only for the ITT patients in the 6-month treatment phase unless otherwise specified. Table CGAN. 5.8 provides definitions for each subgroup variable. Subgroup variables are usually selected if they are potentially prognostic or predictive. A subgroup variable is prognostic if values of the subgroup variable predict the change in efficacy measures regardless of the treatment group assignment. A subgroup variable is predictive if values of the subgroup variable predict heterogeneous treatment effect. Current understanding is that demographic subgroup variable sex is not prognostic nor predictive. But they are standard subgroup variables needed for regulatory submission. The rest of subgroup variables determined before Visit 3 injection are expected to be prognostic. The purpose of the analyses for these subgroup variables is to assess the consistency of treatment effects across the different values of each subgroup variable.

Table CGAN. 5.8 Definition of Subgroup Variables

Subgroup Variable	Categories
Sex	Male, female
Baseline category of MHD (Visit 2 to Visit 3)	2 levels of baseline migraine frequency : • <8 migraine headache days per 30-day period • >=8 migraine headache days per 30-day period
Treatment resistant status (Visit 1)	Treatment resistant status about whether a patient has failed two or more prophylactic treatments (migraine preventive therapy): Yes vs No
Having aura or not (during baseline Visit 2 to Visit 3 period)	Yes vs No (a patient with aura is defined as a patient who answers "yes" to at least one day of ePRO Question 12 "Yesterday, did you experience aura?" during prospective baseline period)
Baseline anti-drug antibody status (Visit 3)	Any confirmed positive anti-drug antibody at baseline (Yes vs No)
Neutralizing anti-drug antibody status (SP II and SP III)	Any positive neutralizing anti-drug antibody time point (Yes vs No) – note that neutralizing anti-drug antibody assays are performed only on confirmed-positive anti-drug antibodies
Treatment-emergent anti-drug antibody status (SP III)	Any treatment-emergent anti-drug antibody (Yes vs No)
Baseline body weight (last observation before Visit 3 injection)	2 levels (weight <= median, median < weight).

Abbreviations: MHD = migraine headache days.

For subgroup analyses, the subgroup-by-treatment interaction will be tested at a 2-sided 0.1 significance level. Treatment group differences will be evaluated within each category of the subgroup variable.

The subgroup analyses for primary will be conducted using MMRM. The same MMRM model as described in Section 5.5.10.1 will be used with terms of subgroup, subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions added as additional covariates. In this analysis, the p-value for the subgroup-by-treatment, subgroup-by-month, and subgroup-by-treatment-by-month interactions will be reported.

For the analysis within a subgroup using MMRM, the LSMean change estimates as well as the treatment comparisons within each subgroup will be conducted with the data within that specific subgroup. The MMRM model will be the same as described in Section 5.5.10.1. For each category of the subgroup variable, comparisons between each treatment group with placebo will be assessed during the 6-month post-baseline period.

50% response rate (one of the key secondary analysis) will be performed by the treatment resistant status subgroup, (simply using 2 different subgroups with the same covariates)

5.6. Interim Analyses

An interim analysis is planned when all randomized patients have had the chance to complete or discontinue 6 months of treatment (SP III) and, thus, will be the final analysis of the primary efficacy endpoint. The interim analysis will be conducted by internal unblinded study team members who do not have direct interaction with sites (Section 5.7). The primal intention of the interim analysis will be for Japan regulatory submission.

5.7. Unblinding Plan

During the study, some members are unblinded (Table CGAN. 5.9). These members will not be allowed to join meetings which may affect the other members' blind condition, such as trail level safety review (TLSR) and data review meetings.

Table CGAN. 5.9 Unblinded members through CGAN Study

Role	Reason	Data source for unblinding
Product Delivery personnel	To provide and manage Clinical trial materials	e-CTS
Clinical Laboratory Operations	To manage and track sample shipping	CLRM
Unblind Case Manager	To report SAE with unblinded information to EU authority	e-CTS
Data Movement	To transfer unblinded data at the timing of interim DBL (and final DBL)	source data of CLUWE

Abbreviations: CLRM = Clinical Laboratory Results Modernization; DBL = database lock; e-CTS = Enhanced Clinical Trials System; EU = European Union; GPS = Global Patient Safety; IWRS = interactive web-response system; PK/PD = pharmacokinetics/ pharmacodynamics; SAE = Serious Adverse Event.

The interim analysis will be conducted by selected unblinded study team members who do not have direct interaction with sites (Table CGAN. 5.10). These members will become unblinded after the interim database lock. All study personnel with direct interaction with sites are kept blinded to the interim analysis results.

Table CGAN. 5.10 Unblinded members after the interim database lock

Role	Reason	Data source for unblinding
Project Statistician	CSR/PMDA consultation preparation	CLUWE/TFL
Statistical Analyst	CSR/PMDA consultation preparation	CLUWE/TFL
Statistical Analysis programmers	CSR/PMDA consultation preparation	CLUWE/TFL
Medicals (Clinical Research Scientist, Clinical Research Physician)	CSR/PMDA consultation preparation	TFL
PK/PD	CSR/PMDA consultation preparation	CLUWE/TFL
Medical Writer	CSR/PMDA consultation preparation	TFL
CPM	CSR/PMDA consultation preparation	TFL
CTPM	CSR/PMDA consultation preparation	TFL
PPM	CSR/PMDA consultation preparation	TFL
Regulatory	CSR/PMDA consultation preparation	TFL
Data Management	CSR/PMDA consultation preparation	CLUWE/TFL

Abbreviations: CPM = Clinical Project Manager; CLUWE = Clinical Users Working Environment; CSR = Clinical Study Report; CTPM = Clinical Trial Project Management; PK/PD = pharmacokinetics/ pharmacodynamics; PMDA = Pharmaceuticals and Medical Devices Agency; PPM = Product Project Manager; TFL = tables, figures, listings;

5.8. Reports to be Generated at Interim and Final Database Lock

5.8.1. Report to be Generated at Interim Analysis

At the time of interim analysis, all randomized patients will have had the chance to complete 6 months of treatment. The following analyses will be conducted for pre-specified population (e.g. ITT, safety population) in the SAP who have had a chance to complete 6 months of treatment:

- Patient disposition as specified in Section 5.5.2, but for Study Period III only.
- Protocol deviations as specified in Section 5.5.3, but for Study Period III only.
- Patient Characteristics as specified in Section 5.5.4.
- Exposure to Investigational Product as specified in Section 5.5.5.

- Treatment Compliance as specified in Section 5.5.6.
- ePRO Diary Compliance as specified in Section 5.5.7, but for Study Period III only.
- Previous Migraine Prevention Therapy and Previous Migraine Acute Treatment as specified in Section 5.5.8.
- Concomitant Therapy, Migraine Prevention Therapy and Migraine Acute Treatment as specified in Section 5.5.9, but for Study Period III only.
- All efficacy, quality-of-life and safety analyses as specified in Section 5.5.10, Section 5.5.11 and Section 5.5.12, but for Study Period III only except immunogenicity related analysis. Immunogenicity related analysis will not be conducted at the interim DBL because some data during SP III will not be included in the interim DBL due to time lag.
- Subgroup analyses as specified in Section 5.5.13.
- Bridging Criteria as specified in Section 5.10.

Some TFLs at interim analysis may contains both SP III and SP IV data (e.g. HCRU summary). Those TFLs will be updated at the final DBL.

Analysis for "SPIII and SP IV combined" and "SP IV only" (e.g. time from the end of SP III to start of migraine prevention treatment in SP IV), and ADA related analysis will be based on the final DBL.

The TFLs for SP III only (i.e. no use of SP IV data) based on the interim DBL will be used in the final study Clinical Study Report (CSR) except for some TFLs needed to be updated. Hence analysis conducted at the interim DBL which do not include SP IV data will not be refresh at the final DBL unless otherwise specified. Those TFLs will be specified and explained in CSR, if they exist.

5.8.2. Report to be Generated at Final Database Lock

For the final database lock, all TFLs will be created except for those which will be created and finalized at the interim analysis. At the timing of final database lock all randomized patients will have had a chance to complete or discontinue 6 months of treatment period (SP III) and 4 months of the post-treatment period (SP IV.)

Analyses at final lock combined with the analysis from interim analysis will be used in the final CSR.

5.9. 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 (SP III and SP IV separately).

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

5.10. Bridging Criteria

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6. References

Diggle P, Kenward M. Informative dropout in longitudinal data analysis (with discussion). *Appl. Stat*. 1994;43:49-93.

Diggle P, Liang K, Zeger S. Analysis of Longitudinal Data. Oxford: Clarendon Press; 1994.

Dunnett CW. A multiple comparison procedure for comparing several treatments with a control. *J Amer Stat Assoc*. 1955;50:1096-1121.

[ICHD-3] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013;33(9):629-808.

Kalali A. Patient satisfaction with, and acceptability of, atypical antipsychotics. *Curr Med Res Opin*. 1999;15(2):135-137.

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

Lipton RB, Varon SF, Grosberg B, McAllister PJ, Freitag F, Aurora SK, Turkel CC. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology*. 2011;77(15):1465-1472.

Permutt T. 2015. Sensitivity analysis for missing data in regulatory submissions. *Stat Med*. 35:2876-2879.